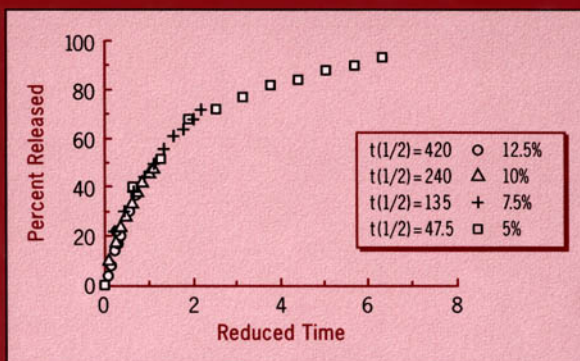


VISIT...

LANZAROTE
Caliente.COM

Advanced Pharmaceutical Solids



Jens T. Carstensen

Advanced Pharmaceutical Solids

DRUGS AND THE PHARMACEUTICAL SCIENCES

James Swarbrick, Executive Editor

AAI, Inc.

Wilmington, North Carolina

Advisory Board

Larry L. Augsburger	David E. Nichols
University of Maryland	Purdue University
Baltimore, Maryland	West Lafayette, Indiana

Douwe D. Breimer	Stephen G. Schulman
Gorlaeus Laboratories	University of Florida
Leiden, The Netherlands	Gainesville, Florida

Trevor M. Jones	Jerome P. Skelly
The Association of the	Alexandria, Virginia
British Pharmaceutical Industry	
London, United Kingdom	

Hans E. Junginger	Felix Theeuwes
Leiden/Amsterdam Center	Alza Corporation
for Drug Research	Palo Alto, California
Leiden, The Netherlands	

Vincent H. L. Lee	Geoffrey T. Tucker
University of Southern California	University of Sheffield
Los Angeles, California	Royal Hallamshire Hospital
	Sheffield, United Kingdom

Peter G. Welling
Institut de Recherche Jouveinal
Fresnes, France

DRUGS AND THE PHARMACEUTICAL SCIENCES

A Series of Textbooks and Monographs

edited by

James Swarbrick

AAI, Inc.

Wilmington, North Carolina

1. Pharmacokinetics, *Milo Gibaldi and Donald Perrier*
2. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
3. Microencapsulation, *edited by J. R. Nixon*
4. Drug Metabolism: Chemical and Biochemical Aspects, *Bernard Testa and Peter Jenner*
5. New Drugs: Discovery and Development, *edited by Alan A. Rubin*
6. Sustained and Controlled Release Drug Delivery Systems, *edited by Joseph R. Robinson*
7. Modern Pharmaceutics, *edited by Gilbert S. Banker and Christopher T. Rhodes*
8. Prescription Drugs in Short Supply: Case Histories, *Michael A. Schwartz*
9. Activated Charcoal: Antidotal and Other Medical Uses, *David O. Cooney*
10. Concepts in Drug Metabolism (in two parts), *edited by Peter Jenner and Bernard Testa*
11. Pharmaceutical Analysis: Modern Methods (in two parts), *edited by James W. Munson*
12. Techniques of Solubilization of Drugs, *edited by Samuel H. Yalkowsky*
13. Orphan Drugs, *edited by Fred E. Karch*
14. Novel Drug Delivery Systems: Fundamentals, Developmental Concepts, Biomedical Assessments, *Yie W. Chien*
15. Pharmacokinetics: Second Edition, Revised and Expanded, *Milo Gibaldi and Donald Perrier*
16. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Second Edition, Revised and Expanded, *Sidney H. Willig, Murray M. Tuckerman, and William S. Hitchings IV*
17. Formulation of Veterinary Dosage Forms, *edited by Jack Blodinger*
18. Dermatological Formulations: Percutaneous Absorption, *Brian W. Barry*
19. The Clinical Research Process in the Pharmaceutical Industry, *edited by Gary M. Matoren*
20. Microencapsulation and Related Drug Processes, *Patrick B. Deasy*
21. Drugs and Nutrients: The Interactive Effects, *edited by Daphne A. Roe and T. Colin Campbell*
22. Biotechnology of Industrial Antibiotics, *Erick J. Vandamme*
23. Pharmaceutical Process Validation, *edited by Bernard T. Loftus and Robert A. Nash*

24. Anticancer and Interferon Agents: Synthesis and Properties, *edited by Raphael M. Ottenbrite and George B. Butler*
25. Pharmaceutical Statistics: Practical and Clinical Applications, *Sanford Bolton*
26. Drug Dynamics for Analytical, Clinical, and Biological Chemists, *Benjamin J. Gudzinowicz, Burrows T. Younkin, Jr., and Michael J. Gudzinowicz*
27. Modern Analysis of Antibiotics, *edited by Adjoran Aszalos*
28. Solubility and Related Properties, *Kenneth C. James*
29. Controlled Drug Delivery: Fundamentals and Applications, Second Edition, Revised and Expanded, *edited by Joseph R. Robinson and Vincent H. Lee*
30. New Drug Approval Process: Clinical and Regulatory Management, *edited by Richard A. Guarino*
31. Transdermal Controlled Systemic Medications, *edited by Yie W. Chien*
32. Drug Delivery Devices: Fundamentals and Applications, *edited by Praveen Tyle*
33. Pharmacokinetics: Regulatory • Industrial • Academic Perspectives, *edited by Peter G. Welling and Francis L. S. Tse*
34. Clinical Drug Trials and Tribulations, *edited by Allen E. Cato*
35. Transdermal Drug Delivery: Developmental Issues and Research Initiatives, *edited by Jonathan Hadgraft and Richard H. Guy*
36. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms, *edited by James W. McGinity*
37. Pharmaceutical Pelletization Technology, *edited by Isaac Ghebre-Sellassie*
38. Good Laboratory Practice Regulations, *edited by Allen F. Hirsch*
39. Nasal Systemic Drug Delivery, *Yie W. Chien, Kenneth S. E. Su, and Shyi-Feu Chang*
40. Modern Pharmaceutics: Second Edition, Revised and Expanded, *edited by Gilbert S. Banker and Christopher T. Rhodes*
41. Specialized Drug Delivery Systems: Manufacturing and Production Technology, *edited by Praveen Tyle*
42. Topical Drug Delivery Formulations, *edited by David W. Osborne and Anton H. Amann*
43. Drug Stability: Principles and Practices, *Jens T. Carstensen*
44. Pharmaceutical Statistics: Practical and Clinical Applications, Second Edition, Revised and Expanded, *Sanford Bolton*
45. Biodegradable Polymers as Drug Delivery Systems, *edited by Mark Chasin and Robert Langer*
46. Preclinical Drug Disposition: A Laboratory Handbook, *Francis L. S. Tse and James J. Jaffe*
47. HPLC in the Pharmaceutical Industry, *edited by Godwin W. Fong and Stanley K. Lam*
48. Pharmaceutical Bioequivalence, *edited by Peter G. Welling, Francis L. S. Tse, and Shrikant V. Dinghe*
49. Pharmaceutical Dissolution Testing, *Umesh V. Banakar*
50. Novel Drug Delivery Systems: Second Edition, Revised and Expanded, *Yie W. Chien*
51. Managing the Clinical Drug Development Process, *David M. Cocchetto and Ronald V. Nardi*
52. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Third Edition, *edited by Sidney H. Willig and James R. Stoker*
53. Prodrugs: Topical and Ocular Drug Delivery, *edited by Kenneth B. Sloan*
54. Pharmaceutical Inhalation Aerosol Technology, *edited by Anthony J. Hickey*

55. Radiopharmaceuticals: Chemistry and Pharmacology, *edited by Adrian D. Nunn*
56. New Drug Approval Process: Second Edition, Revised and Expanded, *edited by Richard A. Guarino*
57. Pharmaceutical Process Validation: Second Edition, Revised and Expanded, *edited by Ira R. Berry and Robert A. Nash*
58. Ophthalmic Drug Delivery Systems, *edited by Ashim K. Mitra*
59. Pharmaceutical Skin Penetration Enhancement, *edited by Kenneth A. Walters and Jonathan Hadgraft*
60. Colonic Drug Absorption and Metabolism, *edited by Peter R. Bieck*
61. Pharmaceutical Particulate Carriers: Therapeutic Applications, *edited by Alain Rolland*
62. Drug Permeation Enhancement: Theory and Applications, *edited by Dean S. Hsieh*
63. Glycopeptide Antibiotics, *edited by Ramakrishnan Nagarajan*
64. Achieving Sterility in Medical and Pharmaceutical Products, *Nigel A. Halls*
65. Multiparticulate Oral Drug Delivery, *edited by Isaac Ghebre-Sellassie*
66. Colloidal Drug Delivery Systems, *edited by Jörg Kreuter*
67. Pharmacokinetics: Regulatory • Industrial • Academic Perspectives, Second Edition, *edited by Peter G. Welling and Francis L. S. Tse*
68. Drug Stability: Principles and Practices, Second Edition, Revised and Expanded, *Jens T. Carstensen*
69. Good Laboratory Practice Regulations: Second Edition, Revised and Expanded, *edited by Sandy Weinberg*
70. Physical Characterization of Pharmaceutical Solids, *edited by Harry G. Brittain*
71. Pharmaceutical Powder Compaction Technology, *edited by Göran Alderborn and Christer Nyström*
72. Modern Pharmaceutics: Third Edition, Revised and Expanded, *edited by Gilbert S. Banker and Christopher T. Rhodes*
73. Microencapsulation: Methods and Industrial Applications, *edited by Simon Benita*
74. Oral Mucosal Drug Delivery, *edited by Michael J. Rathbone*
75. Clinical Research in Pharmaceutical Development, *edited by Barry Bleidt and Michael Montagne*
76. The Drug Development Process: Increasing Efficiency and Cost-Effectiveness, *edited by Peter G. Welling, Louis Lasagna, and Umesh V. Banakar*
77. Microparticulate Systems for the Delivery of Proteins and Vaccines, *edited by Smadar Cohen and Howard Bernstein*
78. Good Manufacturing Practices for Pharmaceuticals: A Plan for Total Quality Control, Fourth Edition, Revised and Expanded, *Sidney H. Willig and James R. Stoker*
79. Aqueous Polymeric Coatings for Pharmaceutical Dosage Forms: Second Edition, Revised and Expanded, *edited by James W. McGinity*
80. Pharmaceutical Statistics: Practical and Clinical Applications, Third Edition, *Sanford Bolton*
81. Handbook of Pharmaceutical Granulation Technology, *edited by Dilip M. Parikh*
82. Biotechnology of Antibiotics: Second Edition, Revised and Expanded, *edited by William R. Strohl*

83. Mechanisms of Transdermal Drug Delivery, *edited by Russell O. Potts and Richard H. Guy*
84. Pharmaceutical Enzymes, *edited by Albert Lauwers and Simon Scharpé*
85. Development of Biopharmaceutical Parenteral Dosage Forms, *edited by John A. Bontempo*
86. Pharmaceutical Project Management, *edited by Tony Kennedy*
87. Drug Products for Clinical Trials: An International Guide to Formulation • Production • Quality Control, *edited by Donald C. Monkhouse and Christopher T. Rhodes*
88. Development and Formulation of Veterinary Dosage Forms: Second Edition, Revised and Expanded, *edited by Gregory E. Hardee and J. Desmond Baggot*
89. Receptor-Based Drug Design, *edited by Paul Leff*
90. Automation and Validation of Information in Pharmaceutical Processing, *edited by Joseph F. deSpautz*
91. Dermal Absorption and Toxicity Assessment, *edited by Michael S. Roberts and Kenneth A. Walters*
92. Pharmaceutical Experimental Design, *Gareth A. Lewis, Didier Mathieu, and Roger Phan-Tan-Luu*
93. Preparing for FDA Pre-Approval Inspections, *edited by Martin D. Hynes III*
94. Pharmaceutical Excipients: Characterization by IR, Raman, and NMR Spectroscopy, *David E. Bugay and W. Paul Findlay*
95. Polymorphism in Pharmaceutical Solids, *edited by Harry G. Brittain*
96. Freeze-Drying/Lyophilization of Pharmaceutical and Biological Products, *edited by Louis Rey and Joan C. May*
97. Percutaneous Absorption: Drugs—Cosmetics—Mechanisms—Methodology, Third Edition, Revised and Expanded, *edited by Robert L. Bronaugh and Howard I. Maibach*
98. Bioadhesive Drug Delivery Systems: Fundamentals, Novel Approaches, and Development, *edited by Edith Mathiowitz, Donald E. Chickering III, and Claus-Michael Lehr*
99. Protein Formulation and Delivery, *edited by Eugene J. McNally*
100. New Drug Approval Process: Third Edition: The Global Challenge, *edited by Richard A. Guarino*
101. Peptide and Protein Drug Analysis, *edited by Ronald E. Reid*
102. Transport Processes in Pharmaceutical Systems, *edited by Gordon Amidon, Ping I. Lee, and Elizabeth M. Topp*
103. Excipient Toxicity and Safety, *edited by Myra L. Weiner and Lois A. Kotkoskie*
104. The Clinical Audit in Pharmaceutical Development, *edited by Michael R. Hamrell*
105. Pharmaceutical Emulsions and Suspensions, *edited by Francoise Nielloud and Gilberte Marti-Mestres*
106. Oral Drug Absorption: Prediction and Assessment, *edited by Jennifer B. Dressman and Hans Lennernäs*
107. Drug Stability: Principles and Practices, Third Edition, Revised and Expanded, *edited by Jens T. Carstensen and C. T. Rhodes*
108. Containment in the Pharmaceutical Industry, *edited by James Wood*
109. Good Manufacturing Practices for Pharmaceuticals: Fifth Edition, Revised and Expanded, *Sidney H. Willig*
110. Advanced Pharmaceutical Solids, *Jens T. Carstensen*

ADDITIONAL VOLUMES IN PREPARATION

Handbook of Pharmaceutical Analysis, *edited by Lena Ohannesian and Anthony J. Streeter*

Pharmaceutical Process Engineering, *Anthony J. Hickey and David Ganderton*

Endotoxins: Pyrogens, LAL Testing, and Depyrogenation, Second Edition, Revised and Expanded, *Kevin L. Williams*

This Page Intentionally Left Blank

Advanced Pharmaceutical Solids

Jens T. Carstensen
University of Wisconsin—Madison
Madison, Wisconsin



MARCEL DEKKER, INC.

NEW YORK • BASEL

ISBN: 0-8247-0431-2

This book is printed on acid-free paper.

Headquarters

Marcel Dekker, Inc.
270 Madison Avenue, New York, NY 10016
tel: 212-696-9000; fax: 212-685-4540

Eastern Hemisphere Distribution

Marcel Dekker AG
Hutgasse 4, Postfach 812, CH-4001 Basel, Switzerland
tel: 41-51-261-8482; fax: 41-51-261-8896

World Wide Web

<http://www.dekker.com>

The publisher offers discounts on this book when ordered in bulk quantities. For more information, write to Special Sales/Professional Marketing at the headquarters address above.

Copyright © 2001 by Marcel Dekker, Inc. All Rights Reserved.

Neither this book nor any part may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopying, microfilming, and recording, or by any information storage and retrieval system, without permission in writing from the publisher.

Current printing (last digit):
10 9 8 7 6 5 4 3 2 1

PRINTED IN THE UNITED STATES OF AMERICA

To my wife

Catherine Gene Karr

with gratitude for her
understanding, support, and love

This Page Intentionally Left Blank

Preface

This book is an outgrowth of my notes for a graduate course given at the University of Wisconsin for several decades. It focuses on the *principles* of the science of pharmaceutical sciences, not necessarily on details or particular examples, except when they are supportive material for the text.

The solids area of the pharmaceutical sciences has been explored more often in the last decade than in prior times. This, in particular, is due to the advent of sophisticated instrumentation and computer access. However, such advantages can lead to a certain mental laziness, and much of what is written in today's literature is disregarding, in fact at times ignorant, of the principles on which the instruments and programs are based, and much misinterpretation occurs. Parts of this book address this aspect. In so doing, the references are often not new, but rather give credit to the scientists of yore who really were the innovators.

The book also presents some entirely new aspects, not previously published, concerning the proper basic consideration in the approach to certain areas of pharmaceutical solid science.

The book is written for those who are interested in the actual processes on the microscopic level, with particular emphasis on elucidating models for systems so that they can be of general use. The book should appeal to pharmaceutical scientists in industry, as well as the more sophisticated segment of pharmaceutical manufacturing personnel. It should appeal to scientists in government agencies, for it pinpoints problem areas that might have bearing on, for example, New Drug Applications (NDAs). It should have appeal to attorneys in patent law as well as patent examiners, because it elucidates whether a given type of solution to a problem is really patentable. Also, it should be appealing to graduate students and to advanced undergraduate students who desire a place in the pharmaceutical solid sciences area.

Jens T. Carstensen

This Page Intentionally Left Blank

Contents

<i>Preface</i>	v
1. One Component Systems	1
2. Properties of Solids	13
3. Solubility	27
4. Particle Sizes and Diameters	51
5. Micromeritics	61
6. Crystallization	89
7. Amorphates	107
8. Polymorphism	117
9. Moisture Isotherms with Crystalline Solids	133
10. Drug Substance Considerations	159
11. Melting Point Diagrams and Eutectics	169
12. Dissolution from Particles and Surfaces	191
13. Dissolution from Polydisperse Populations	209
14. Solid State Stability	223
15. Effect of Moisture on Solid-State Stability	267
16. Apparent Volumes and Densities	281

17. Cohesion	299
18. Powder Flow	309
19. Comminution	323
20. Blending	335
21. Wet Granulation	353
22. Hard Shell Capsules	375
23. Tablet Physics	387
24. Physical Principles of Tablets	407
25. Disintegration and Dissolution	427
26. Polymers	439
27. Coating of Tablets	455
28. Single Unit Sustained Release Dosage Forms	469
29. Sustained Release by Microencapsulation	493
<i>Index</i>	<i>511</i>

One-Component Systems

1.1. States of Matter	2
1.2. Some Thermodynamic Functions	2
1.3. Gibbs' Phase Rule	3
1.4. X-Ray Crystallography	4
1.5. Methods	6
1.6. Inorganic Lattices: Radius Ratio Rule	6
1.7. Introduction to Polymorphism	7
1.8. Lattice Energy, for Ionic Compounds	8
Symbols	11
References	11

The purpose of pharmaceutical research is to explore the causes of properties of dosage forms, in this case, solid dosage forms. The properties of the dosage form, and a host of its qualities are a function of the neat drug. Characterization of the dosage form, therefore, requires characterization of the drug substance and what its properties are, so that the sources of derivative properties in the dosage form can be adequately assigned. It is granted that such sourcing is never complete. Is the dissolution rate of a drug in a dosage form, for instance, a function of the dissolution rate of the drug substance, or is it influenced more by the excipients? Such questions cannot be answered a priori, but before an answer is attempted, the dissolution rate of the drug substance must first be known. Hence, this property (and many other) properties of the drug substance must be explored.

Tools exist, nowadays, that allow sharp definition of a solid. Such characterization of solid-state forms encompass microscopy, infrared (IR) spectroscopy, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), Karl Fischer titration, X-ray powder diffraction analysis, single-crystal X-ray diffraction,

and (at times) solution calorimetry (Ledwige, 1996). Reference will be made to these methods in appropriate places in this book.

In solid pharmaceutical-marketed products, both the drug substance and excipients are present. (The word “drug,” at times, also refers to the drug product, although the distinction made in the present text now seems to be the accepted nomenclature.) Much research dealing with pharmaceutical products is directed at the factors that make them possible and also addresses the failures that might or do occur.

Although many such failures stem from manufacturing and excipients, many also stem from the drug substance itself. It is, therefore, of importance to discuss the properties and testing approaches of the neat drug (the “drug,” the “drug substance”) to assess the properties and difficulties associated with the final product (the “dosage form” or the “drug product”).

1.1. STATES OF MATTER

There are three states of matter: (a) gases, (b) liquids, and (c) solids. Their definitions are intuitive, but if defined in words, a *gas* needs a three-dimensional, closed container to contain it, a *liquid* needs simply an open three-dimensional container, and a *solid* simply needs a two-dimensional planar support.

The definition, however, is not specific in the terms of solids. As shall be seen in later chapters, solids are either crystalline or amorphous, and amorphous solids may (above their glass temperature, T_g) be rubbery, and below this temperature, they are glassy. In the rubbery state they are to be likened to (or actually *are*) supercooled melts or liquids and, as such, *are* liquids. In the glassy state, however, a substance will mimic many of the qualities of a crystalline solid; hence it may be considered “solid.” Because liquids have a viscosity, it will, in this text, be conventional to consider a solid a “solid,” even if it is amorphous, if its viscosity is higher than what it is at the glass transition temperature. A viscosity at T_g of 10^{12} Pa s is often used (Lu and Zografi, 1997) and this will be employed here as the cutoff point for a solid.

1.2. SOME THERMODYNAMIC FUNCTIONS

In this book, the following terminology will be used for the four thermodynamic functions: E is free energy, F is Helmholtz free energy, G is Gibbs’ energy, and H is enthalpy, and in differential form they are related as follows, where T is temperature, S is entropy, V is volume, P is pressure:

$$dE = TdS - PdV \quad (1.1)$$

$$dF = -SdT - PdV \quad (1.2)$$

$$dG = -SdT + VdP \quad (1.3)$$

$$dH = TdS + VdP \quad (1.4)$$

The chemical energy terms are not included in the foregoing, but with these, it is in particular Eq. (1.3) that is affected. With this term

$$dG = -SdT + VdP + \sum \mu_i dn_i \quad (1.5)$$

where μ is chemical potential and n is number of i -species transferred. It is particularly noted that $dG = 0$ during equilibrium, and that, for a voluntary process, $dG < 0$. G is a convenient function in that dT and dP are zero at constant temperature and pressure, and that, under these conditions,

$$(dG)_{T,P} = \sum \mu_i dn_i \quad (1.6)$$

Similarly dH is the enthalpy change at constant pressure. An outcome of this is that

$$\Delta G = \Delta H - T\Delta S \quad (1.7)$$

Often, in a chemical situation, at constant T , it is possible to independently determine ΔG and ΔH , and it is then possible to calculate ΔS from

$$\Delta S = \{\Delta H - \Delta G\}/T \quad (1.8)$$

Another frequently employed relation is

$$d\{\Delta G/T\}/dT = -\Delta H/T^2 \quad (1.9)$$

For instance, for a chemical reaction with equilibrium constant K ,

$$\Delta G = -RT \ln[K] \quad (1.10)$$

Inserting Eq. (1.9) into Eq. (1.10) then gives

$$d\{\Delta G/T\}/dT = -Rd \ln[K]/dT = -\Delta H/T^2 \quad (1.11)$$

If $\ln[K]$ is known at several temperatures, ΔH for the reaction may be found, and ΔS may now be found from Eq. (1.8).

Most often, in chemistry, systems are constant-pressure systems. In solids, however, situations arise that call for constant-volume considerations and in this case, the chemical equilibrium criterion is that ΔF , not ΔG , be zero.

It should finally be mentioned that the entropy S , of a system is a measure of its disorder. Boltzmann's law states that:

$$S = k \ln[W] \quad (1.12)$$

where W is the number of ways in which a system can be made up.

1.3. GIBBS' PHASE RULE

It is of interest to estimate the number of phases that can be present under one particular energetic condition. Suppose an ensemble in equilibrium consists of n components, and p phases. Because there is equilibrium between phase 1 and 2, between phase 2 and 3, and so on the following holds.

$$\mu_1 = \mu_2 = \mu_3 = \cdots \mu_l = \cdots \mu_p \quad (1.13)$$

Note that Eq. (1.13) constitute $p - 1$ equations. There are $(p - 1)$ equations for each of the n compounds, so the total number of equations is $n(p - 1)$. Pressure and temperature are variables and there are $(n - 1)$ independent concentrations per

phase, so that the number of variables is $p(n - 1) + 2$. The number of degrees of freedom is the number of variables minus the number of equations, i.e.,

$$df = p(n - 1) + 2 - n(p - 1) = n - p + 2 \quad (1.14)$$

This means that there are df variables that may be changed without the system “losing” a phase.

As an example, a beaker of water has one component, there are two phases (liquid and gas); hence, $n = 1$ and $p = 2$, so that by Eq. (1.14) there is 1 degree of freedom (i.e., one variable [either T or P] may be changed). If the temperature is increased a bit, no phase will be lost. However, it is not possible to change both T and P at will, because a given T dictates a certain P and vice versa.

The situation is different at the freezing point. Here, there are three phases, ice (solid), water (liquid), and vapor. Hence $df = 0$, and neither T nor P may be changed without losing a phase. Increasing the temperature loses the solid phase (the ice melts) and lowering it loses the liquid phase (the water freezes). Such a point is called a *triple point*.

The use of Eq. (1.14) is often difficult and *it is stressed that it applies only to an equilibrium situation*. When in doubt, it is prudent to actually do the derivation leading to Eq. (1.14) for the particular system and obtain $[df - 2]$ as the difference between the number of equations and the number of unknowns. *The term degree of freedom in this context is exactly the opposite of its statistical meanings (where it is the number of points minus the number of equations).*

1.4. X-RAY CRYSTALLOGRAPHY

A lattice is a periodic array. Points in the (ideal) lattice are occupied by molecules or ions, and these may arrange themselves in different fashions (Fig. 1.1).

There are seven different crystal systems, as shown in Table 1.1

Positioning of atoms, molecules, or ions in the lattice may be visualized as a series of layers. Depending on which direction the lattice is viewed, there are different “layers” in different directions. The distance between these layers is denoted d below, and the manner in which d is determined is as follows:

To get an idea, first of all, of the magnitude of d consider a solid compound of molecular weight 180 and a true density of 1.5. The molar volume of such a compound would be $180/1.5 = 120 \text{ cm}^3/\text{mol}$. Because there are 6×10^{23} molecules in a mole, each of these occupies $120/(6 \times 10^{23}) = 200 \times 10^{-24} \text{ cm}^3$. If, for order of mag-

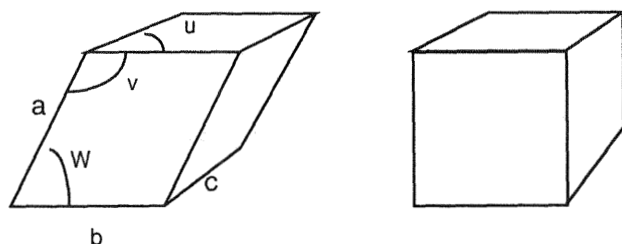


Fig. 1.1 Example of crystal forms. The angles, u , v , and w are shown in the left figures, as are the possible distances, a , b , and c . These are referred to in Table 1.1.

Table 1.1 Crystal Systems

Angle between axes	Length of side distances	System	Alternate name	Examples
$u = v = w = 90^\circ$	$a = b = c$	Regular	Cubic	NaCl
$u = v = w = 90^\circ$	$a = b \neq c$	Tetragonal	Pyramidal	Rutil
$u = v = w = 90^\circ$	$a \neq b \neq c$	Orthorhombic	Rhombic	AgNO ₃
$u = v = 90^\circ \neq w$	$a \neq b \neq c$	Monoclinic		<i>p</i> -Aminobenzoic acid
$u \neq v \neq w \neq 90^\circ$	$a \neq b \neq c$	Triclinic		K ₂ CrO ₇
$u = v = w \neq 90^\circ$	$a = b = c$	Trigonal	Rhombohedral	NaNO ₃
$u = w = 90^\circ$ $w = 120^\circ$	$a = b = c \neq d$	Hexagonal		Graphite

nitude calculations, the arrangement is assumed to be cubic, the side length of the cube encasing the molecule would be given by

$$d^3 = 200 \times 10^{-24} \text{ cm}^3$$

(1.15)

or

$$d = 5.85 \times 10^{-8} \text{ cm}^3 = 5.85 \text{ \AA}$$

(1.16)

where 1 Å is defined as 10⁻⁸ cm³. X-rays are of this order of magnitude and are used for measurement of atomic, molecular, and ionic distances within a lattice.

This is performed according to Bragg’s law, which relies on the fact, that when two X-rays are in-phase, they will then reinforce one another, and the principle on which it is carried out is shown in Fig. 1.2.

Two X-rays, 1 and 2, strike a surface at an angle of *U* . Ray 2 traverses a distance ABC (in bold in the figure) longer than ray 1; hence, for them to be in-phase, this distance must be a multiple of the wavelength λ of the ray. The distance ABC can be shown, by simple trigonometry, to be equal to 2*d* sin[*U*] i.e., for attenuation to be monitored at the collector *Q*, this distance must be equal to *n*λ; that is,

$$2d \sin[U] = n\lambda$$

(1.17)

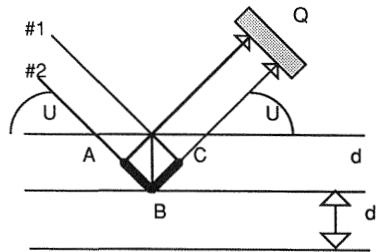


Fig. 1.2 Schematic for Bragg’s law. The incident angle, *U*, equaling the reflected angle, *U*, is usually referred to as θ.

Ledwidge et al. (1996), for instance, reports an X-ray diffraction pattern (using Cu $K\alpha$ -X rays with $\lambda = 1.5418 \text{ \AA}$) of diclofenac *N*-(2-hydroxyethyl)pyrrolidine and the smallest 2θ -value where a peak occurs is 7.6° . The *distance* (i.e., the *d*-value) corresponding to this would be

$$d = 1.54 / (2 \sin 3.8^\circ) = 11.6 \text{ \AA} \quad (1.18)$$

1.5. METHODS

The most common method is *powder X-ray diffraction*. In this method, powder is packed into a cell, and this is subjected to the type of detection shown in Fig. 1.2. Planes present themselves in sufficient abundance to allow determination of the crystal lattice constants without determination of the position and direction of atoms, molecules, or ions in the lattice

Single-crystal X-ray crystallography allows determination of the position and direction of the ions, atoms, and molecules in the lattice. For instance, Turel et al. (1997) used X-ray crystallography to determine the crystal structure of ciprofloxacin hexahydrate, and showed that it exists in zwitterionic form in the solid state. The carboxylic proton is present by the piperazine terminal nitrogen.

Adjunctly, however, they employed IR, Raman spectroscopy, and thermal methods to determine that the water in the hexahydrate was present in a complicated network governed by hydrogen bonding.

1.6. INORGANIC LATTICES: RADIUS RATIO RULE

Inorganic ionic compounds consist of fairly spherical entities, and their packing is related to the relative radii of the two components of the systems.

Consider, for instance, the situation in Fig. 1.3, in which a compound consists of two ions, one smaller, with radius r , and one larger, with radius R . It is obvious from the figure that the right triangle, ABC has sides, $AB = BC = 2R$ and a hypotenuse, $CA = 2R + 2r$. Hence,

$$(2R)^2 + (2R)^2 = (2R + 2r)^2 \quad (1.19)$$

or

$$r^2 + 2Rr - R^2 = 0 \quad (1.20)$$

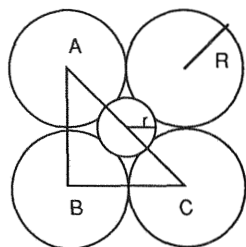


Fig. 1.3 Schematic for derivation of the radius ratio rule.

which has the positive root:

$$r = R(1 - \sqrt{2}) = 0.141R \quad (1.21)$$

Similar relations can be obtained for other arrangements (crystal systems), and the rules in Table 1.2 emerge.

1.7. INTRODUCTION TO POLYMORPHISM

Whereas inorganic compounds often (if not most often) crystallize in one particular crystal system, organic compounds have the capability of crystallizing in several different (*poly*) forms (*morphs*), and this phenomenon is denoted *polymorphism*.

Because there are seven crystal systems, it might be tempting to think that there could, at most, be seven different polymorphs of one compound; however, the number is not limited to that.

The molecules may be in different lattices, because their orientation is different in the two different polymorphs (of the same crystal system). The lattice constants, a , b , and c , then might or would be different.

Polymorphs will be subject to a special chapter (see Chapter 8) but at this point the following will be noted. Of two polymorphs, one (form I) will be (configurationally) more stable than the other (e.g., form II) for the following reasons.

1. There are no rules for the nomenclature I, II, and so on. Often the numbers simply signify the chronological order in which they were produced.
2. The less stable form, at a given temperature, will have a higher vapor pressure.
3. The less stable form, at a given temperature, will have a higher apparent solubility. This concentration of drug in the solvent is reproducible, but the solution is not thermodynamically stable. Eventually precipitation of a more (the more) stable form will occur, and the concentration will level off at the thermodynamic equilibrium solubility.
4. It is not possible, in a practical sense, to talk about the “most stable” polymorph, for a more stable polymorph may be discovered at a later time. From a fictional point of view, this is the subject of the book *Cats*

Table 1.2 Examples of the Radius Ratio Rule Applications

Ratio = r/R	Coordination number	Lattice	Example
0–0.155	2		Carbon dioxide
0.155–0.225	3	Hexagonal	Boron nitride
0.225–0.414	4	Tetrahedral	Zinc blende
0.414–0.733	6	Octahedral	NaCl
0.733–1	8	Body-centered cubic	CsCl ₂
1	12	Face-centered cubic and also hexagonal	

Cradle, by Kurt Vonnegut. Here a more stable, higher-melting form of water (Ice Nine) eventually causes the world's oceans to freeze over.

5. The molecules in solutions created by either a less or more stable polymorph are the same.

1.8. LATTICE ENERGY FOR IONIC COMPOUNDS

The section to follow has been developed quite rigidly for inorganic ions. However, extensions to organic crystals are possible. In the development, the term *particle* will often be used to signify "ion" or in some cases "molecule."

When bonding occurs between two molecules, a minimum will occur in the potential energy curve that exists between them. This distance is known as the lattice constant R_0 (Fig. 1.4).

Energy curves, as a function of atomic or molecular distance, are rationalized (Maron and Prutton, 1965) by the existence of two opposing forces between the atoms or molecules: an attractive force and a repulsive force.

The attractive force is, theoretically, inversely proportional to the seventh power of the interatomic or intermolecular distance. The repulsive term depends on distance by some (the n th) power of the separation. The potential energy u' of the interaction between two neighboring ions, therefore, may be written as

$$u' = (A/r^7) - (B/r^n) \quad (1.22)$$

The value of n is, ordinarily, from 10 to 13.

Each interparticular distance (r_{ij}) is expressed as a number (p_{ij}) multiplied with the separation (R) between two particles. Examplewise, in the situation shown in Fig. 1.5, the j th and the i th molecule would be separated by 2 "units" so that r_{ij} would equal $2R$.

In general this may be written as

$$r_{ij} = p_{ij}R \quad (1.23)$$

Eq. (1.22) is now summed over all interaction possibilities, which then gives the energy, ϕ , for one particle.

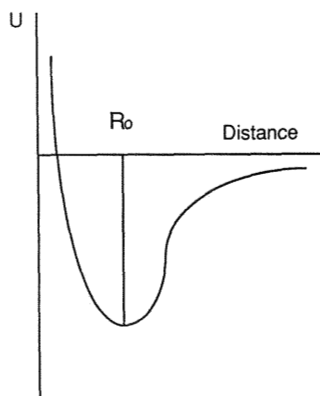


Fig. 1.4 Potential energy curve.

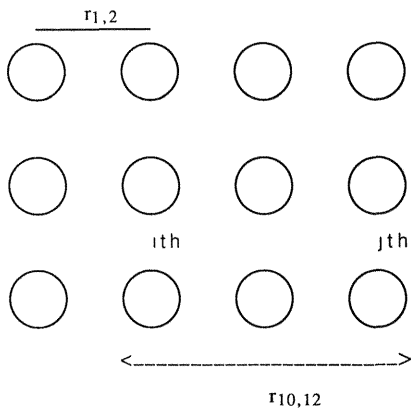


Fig. 1.5 Schematic of interacting atoms or molecules.

$$\phi = (A/R^7) \sum (1/p_{ij}^7) - (B/R^n) \sum (1/p_{ij}^n) \quad (1.24)$$

where summation is over all $i \neq j$. The following terms are introduced for the sake of convenience:

$$a = \sum (1/p_{ij}^7) \quad (1.25)$$

and

$$b = \sum (1/p_{ij}^n) \quad (1.26)$$

For a given crystal a and b are constants, so that Eq. (1.24) becomes:

$$\phi = (Aa/R^7) - (Bb/R^n) \quad (1.27)$$

The distance at equilibrium, R_0 , is obtained by obtaining the first derivative and equating it to zero (and at the same time ensuring that the second derivative will be positive). Hence,

$$\partial\phi/\partial R = (-7Aa/R^8) + (nBb/R^{n+1}) \quad (1.28)$$

For equilibrium to occur this must be zero, so

$$(-7Aa/R_0^8) + (nBb/R_0^{n+1}) \quad (1.29)$$

or

$$7Aa/R_0^8 = nBb/R_0^{n+1} \quad (1.30)$$

or

$$(7/n)(Aa)/R_0^7 = Bb/R_0^n \quad (1.31)$$

This is now inserted into Eq. (1.27) to give

$$\phi_0 = [Aa/R_0^7] - [(7/n)(Aa)/R_0^7] = [Aa/R_0^7][1 - (7/n)] \quad (1.32)$$

The energy per mole U can now be obtained by multiplication of ϕ_0 , with the Avogadro number N , so that

$$U = N[Aa/R_0^7]\{1 - (7/n)\} \quad (1.33)$$

Conventionally, U is equated with the enthalpy of sublimation, because solids are considered constant-volume (rather than constant-pressure) situations. The actual value of a is obtained geometrically. For ions, the terms alternate in sign (each second ion being negative, thus exerting attraction, each second being opposite in sign and giving rise to attraction). For molecules (many organic molecules) the force terms are all positive. The large negative value of n , the exponent in the second term in Eq. (1.27), it is most often acceptable to use only one or two terms making the summation fairly simple.

R_0 values may be obtained by X-ray analysis, leaving but two unknowns, A and n in Eq. (1.33). The value of n may be obtained by low-temperature compressibility measurements. The definition for compressibility k , is

$$k = -(1/V)dV/dP \quad (1.34)$$

At low temperature, the T term in the definition for U vanishes so that

$$dU = -PdV, \quad (1.35)$$

so that

$$1/k = Vd^2U/dV^2 \quad (1.36)$$

Molar volume with the nomenclature used here is

$$V = NR^3 \quad (1.37)$$

so that

$$dU/dV = (dU/dR)(dR/dV) \quad (1.38)$$

The second derivative, hence, is

$$d^2U/dV^2 = (dU/dR)(d^2R/dV^2) + (d^2U/dR^2)(dR/dV)^2 \quad (1.39)$$

At equilibrium, $dU/dR = 0$, so that the first term vanishes, reducing Eq. (1.39) to

$$d^2U/dV^2 = (d^2U/dR^2)(dR/dV)^2 \quad (1.40)$$

From Eq. (1.36) we have

$$(dR/dV)^2 = (3NR^2)^2 = 9N^4R^4 \quad (1.41)$$

so Eq. (1.40) becomes

$$d^2U/dV^2 = (d^2U/dR^2)(9N^4R^4) \quad (1.42)$$

This is combined with Eq. (1.36) to give

$$1/k = (1/NR_0^3)(9N^4R_0^4)(d^2U/dR^2) = 9N^3R_0^3(d^2U/dR^2) \quad (1.43)$$

Equation (1.43) when differentiated twice gives

$$d^2U/dR^2 = 56(NAa)[1 - (7/n)](R_0^9) \quad (1.44)$$

which inserted in Eq. (1.43) gives

$$1/k = 504N^4(Aa)[1 - (7/n)](R_0^{12}) \quad (1.45)$$

which allows calculation of n .

SYMBOLS

- A = constant in the energy versus distance equation
 $a = \Sigma(1/p_{ij}^7) =$ Madelung constant
 $b = \Sigma(1/p_{ij}^9) =$ Madelung constant
 B = constant in the energy versus distance equation
 d = distance between molecular layers
 E = energy
 F = Helmholtz energy
 G = Gibbs' energy
 H = enthalpy
 k = (a) Boltzmann's constant; (b) compressibility
 K = equilibrium constant
 N = Avogadro's number
 n = (a) number of particles, ions, molecules; (b) integer in Bragg's law;
 (c) exponent in potential energy versus distance equation.
 P = pressure
 p_{ij} = factor for expressing the distance between the i th and j th ion in units of R
 r_{ij} = distance between the i th and j th ion
 R = (a) distance between particles, ions, molecules; (b) ionic radius of larger ion
 r = ionic radius of a smaller ion
 R_0 = equilibrium distance between particles, ions, molecules
 S = entropy
 T = absolute temperature (K)
 U = crystal energy
 u' = potential energy between two ions
 V = volume
 W = number of ways of building up a system
 μ = chemical potential
 θ = incident angle of an X-ray
 λ = wavelength

REFERENCES

- Benettinetti G, Giordano F, Fronza G, Italia A, Pellegata R, Villa M, Ventura P (1990). *J Pharm Sci* 79:470.
 Carstensen JT (1981). *Solid Pharmaceutics, Mechanical Processes and Rate Phenomena*. Academic Press, New York, pp 6–7.
 Kittel (1962). *Introduction to Solid State Physics*. pp 70–79.
 Ledwidge MT, Draper SM, Wilcock DJ, Corrigan OI (1996). *J Pharm Sci*. 85:16.
 Lu Q, Zografi G (1997). *J Pharm Sci* 86: 1374.
 Maron SM, Prutton CF (1965). "Principles of Physical Chemistry, 4th ed. Macmillan, London, pp 728–729.
 Turel I, Bukovec P, Quirós M (1997). *Int J Pharm* 152:59.

This Page Intentionally Left Blank

2

Properties of Solids

2.1. Lattice Defects	13
2.2. Density	16
2.3. Classic Heat Capacity	18
2.4. The Einstein Equation	19
2.5. Vapor Pressure	22
2.6. Melting Points	23
2.7. Polymorphism	24
References	25

The text, as mentioned earlier, will deal first with properties of solids that are not, primarily, a function of their subdivision. In essence they may be considered the properties of an infinitely large slab of the solid. Later chapters will deal with properties that are a function of the subdivision of the solid (e.g., particle size).

2.1. LATTICE DEFECTS

Crystals are never perfect. As they grow (a point that will be discussed later) planes may grow over one another on the surface (Fig. 2.1), shunting out areas of voids. They may also grow as a screw (a so-called screw dislocation), and in this case there is a sort of pore that penetrates the crystal as the axis of the screw. Several types of defects are depicted in Figs. 2.2 and 2.3.

From a statistical-mechanical point of view, defects are to be expected. The development of this concept in the following is based on the Schottky defect, but it would also apply to vacancies of other natures. Suppose (Fig. 2.3), that a crystal contains nine molecules. There is but one way of arranging them. If one of the internal molecules is moved to the surface, there will be $\{10_1\} = 10$ ways of doing

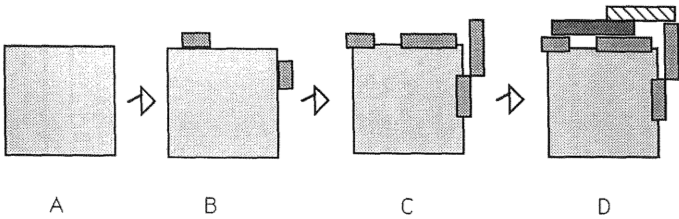


Fig. 2.1 A nucleus or crystal (A) grows on the surface, and two sites are shown. Further growth and a site in a second layer are shown in (C) and in (D) the growth in “higher” sites grow over the lower sites creating a “hole.”

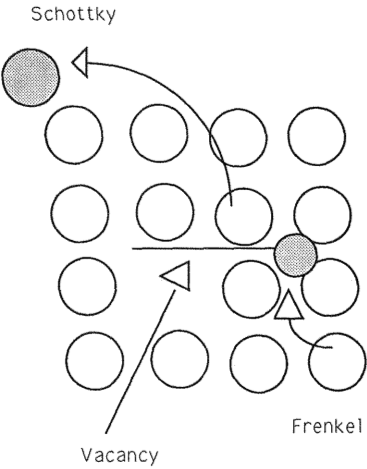


Fig. 2.2 Frenkel, Schottky, and screw defects.

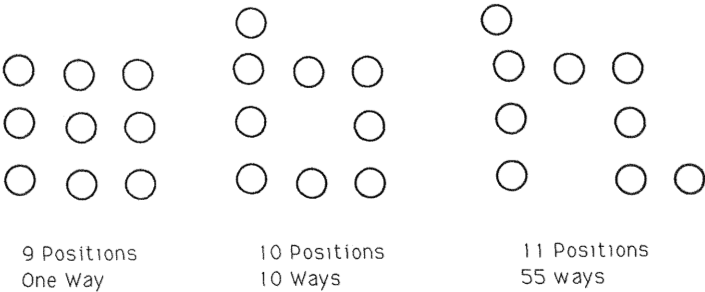


Fig. 2.3 Situation where one and two Schottky defects are created in a crystal with (originally) nine lattice sites.

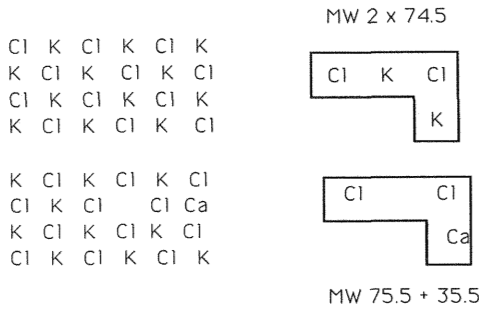


Fig. 2.4 Calcium replacing K as a means of creating a vacancy.

this. If two molecules were moved to the surface, then the number of ways would be $\{11_2\} = 11 \times 10/2 = 55$ ways.

The Boltzmann law states that the entropy of a system S is proportional to the logarithm of the number of ways in which it can be made up:

$$S = k \ln(\text{ways the system can be made up}) \quad (2.1)$$

where k is the Boltzmann constant. For a system of $N + n$ positions with n vacancies, the entropy would be

$$S = k \ln[(N + n)! / \{N!n!\}] \quad (2.2)$$

Use is now made of Sterling's formula

$$\ln N! = N \ln N - N \quad (2.3)$$

i.e., as applied to this system

$$\ln[(N + n)! / \{N!n!\}] = N \ln N - (N - n) \ln(N - n) - n \ln(n) \quad (2.4)$$

so that

$$S = k\{N \ln N - (N - n) \ln(N - n) - n \ln(n)\} \quad (2.5)$$

Solid systems are usually considered constant volume systems, so that in equilibrium considerations, it is the Helmholtz free energy (rather than the Gibbs energy) that is applied.

$$F = nE_s - TS \quad (2.6)$$

where E_s is the energy associated with one vacancy. This is now differentiated relative to n to give the equilibrium condition:

$$dF/dn = E_s - kT \ln[(N - n)/n] = 0 \quad (2.7)$$

where the argument is Eq. (2.5) differentiated relative to n . This rearranges to:

$$E_s = -kT \ln(n/[N - n]) \quad (2.8)$$

or

$$n = Ne^{-E_s/kT} \quad (2.9)$$

Normal range of vacancies is of the order of 0.001%.

Defects are often created by doping (i.e., introducing a foreign molecule into the lattice of the compound in question). For instance, with KCl, the potassium ion (MW 39) may be replaced with relative ease by a calcium ion (MW 40), because their sizes are approximately equal. If one considers a crystal with N ions of KCl, then each time a calcium ion (MW 40) is introduced, a hole with one missing K (MW 39) is created. The loss in weight, therefore, is 38 per calcium ion. If there are n calcium ions in a crystal with N positive ion sites, then the density is calculated as follows (Figs. 2.4 and 2.5).

The weight, W_- without vacancies, should be (MW of Cl being 35.5)

$$W_- = 2(N + n)74.5 \quad (2.10)$$

The weight W_+ with vacancies would be

$$W_+ = 2N74.5 + n75.5 + n35.5 \quad (2.11)$$

The difference between these two numbers is

$$\Delta W = -38n \quad (2.12)$$

The volume of the crystal is $N \times V$, where V is the molecular volume, so that the difference in density would be

$$\Delta W/N = -38n/NV \quad (2.13)$$

Hüttenrauch (1983), Hüttenrauch and Keiner (1979 a,b), Longuemard et al. (1998), Hersey and Krycer (1981), Moriata et al. (1984), Grant and York (1986), and Vachon and Grant (1987) have called attention to the fact that processing of solids causes lattice defects, giving rise to an increase in disorder. Hancock and Zografi (1997) claim that this would give the particle a certain viscoelasticity.

Hiestand (1997) states that “the ever present, plastic deformation profiles an explanation why lot-to-lot problems are common.” The yield value of the particles is dependent on defects in the crystals, and changes may occur in nearly all processing. Usual production specifications do not include criteria for mechanical properties.

2.2. DENSITY

There are several different definitions of *density*. The ideal density of a crystal can be calculated from knowledge of its lattice parameters and the molecular weight.

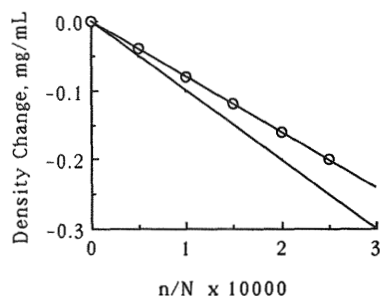


Fig. 2.5 Change in density of KCl doped with calcium ions. The lower line is the theoretical line, the upper line the experimental line. (Data from Pick and Weber, 1950.)

If, for instance, the lattice parameters of a orthorhombic crystal are 5, 7, and 8 Å, and its molecular weight is 240, then the mass of one molecule is $180/(6 \times 10^{23}) = 3 \times 10^{-22}$ g. The volume it occupies is $5 \times 7 \times 8 \times 10^{-24} = 2.8 \times 10^{-22}$ cm³, so that the crystallographic density would be $3/2.8 = 3/1.92 = 1.07$ g/cm³. Nowadays, crystallographic densities are reported routinely in studies of the crystallographic details of a particular form of the compound. As an example, Ceolin (1997) has reported the volume of the triclinic unit cell of carbamazepine to be 2389 Å³.

Because of lattice defects and vacancies, the actual density would be less. The actual particle density is determined by either wet pycnometry or by helium pycnometry (Fig. 2.6).

In wet pycnometry, a liquid in which the solid is insoluble, is selected (e.g., water for a poorly water-soluble compound). The pycnometer has a given volume V cm³, and the weight of the contents W is determined. The pycnometer is filled to a mark giving the density ρ_1 , of the solvent:

$$\rho_1 = W/V \quad (2.14)$$

Now M grams of solid are added, having the (unknown) density of ρ_2 . These M grams occupy M/ρ_2 cm³, so that the liquid now occupies $\{V - (M/\rho_2)\}$ cm³. The net weight (M_2) of the ensemble is obtained experimentally (Fig. 2.7), and is given by

$$M_2 = \{[V - (M/\rho_2)]\rho_1\} + M \quad (2.15)$$

The only unknown is ρ_2 , which is the quantity sought.

Disadvantages are (a) that the solid may be somewhat soluble in the pycnometer liquid, and (b) air entrapment. The former is marginal at best if the solvent is selected with care. At high dilution, ideal solutions are approached, so that the volume contraction or expansion considerations are negligible.

None of these problems exist in the use of the helium pycnometer, which works on the same principle, except the “liquid” is helium.

Therefore, it is not to be expected that the particle density is the “true” density. This could be derived only by knowing the lattice parameters.

Jozwiakowski et al. (1996) reported on the solubility behavior of lamivudine and in this process reported on the lattice constants of the compound. The formula for the compound is C₈N₃H₁₁O₁₆S. The following program in BASIC calculates the molecular weight employing the precise atomic weights

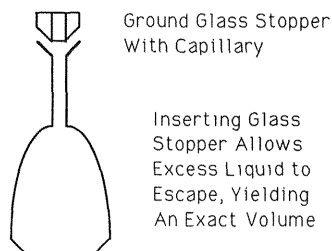


Fig. 2.6 Liquid pycnometer.

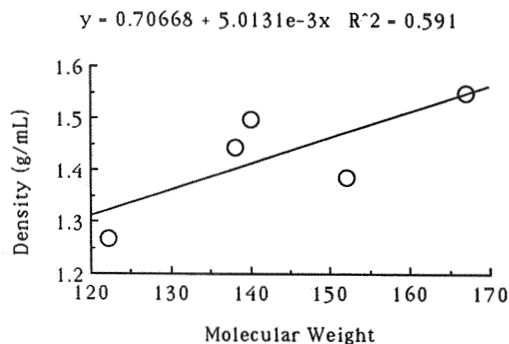


Fig. 2.7 Densities as a function of substituent for a series of monoclinic 4-substituted benzoic acids. (Data from Musa, 1972.)

```

X1 = (8 * 12.01115)
X2 = 3 * 14.0067
X3 = 11 * 1.00797
X4 = 3 * 15.9994
X5 = 32.064
X6 = X1 + X2 + X3 + X4 + X5
PRINT "MW="; X6
Y1 = 10.427
Y2 = 14.327
Y3 = 34.851
Y4 = Y1*Y2*Y3/20
PRINT "MolecVol in A^3="; Y4
Z1 = 6.02252*Y4/10
PRINT "Mol Vol="; Z1
Z2 = Z1/X6
PRINT "Vol/gram="; Z2
Z3 = 1/Z2
PRINT "Cryst. Density="; Z3

```

2.3. CLASSIC HEAT CAPACITY

Heat capacity plays a part in several pharmaceutical considerations on a theoretical plane. If a process goes from stage A to stage B, then

$$A \rightarrow B \quad (2.16)$$

is accompanied by an enthalpy. The process could be, for instance, solubility, and the heat associated with this would be the heat of solution. This is often considered a constant.

The heat capacity C_p of the solution is given by

$$C_p = d\Delta H/dT \quad (2.17)$$

and assuming that it is constant then implies that ΔH is temperature-independent. There is but little difference between C_p and C_v for solids, and they may be interchanged freely.

The considerations to be outlined in the following are mostly based on work with metals, but they translate to organic molecules as well.

The heat capacity is assumed to be associated with the energy E of the molecules in the lattice, and these are assumed to be harmonic oscillators. In classic theory, the average energy of a system is kT per degree of freedom, where k is the Boltzmann constant and T is absolute temperature.

For an ensemble of N harmonic oscillators, with three degrees of freedom (the molecule may oscillate in three directions), the average energy is:

$$E_{\text{avg}} = 3NkT \quad (2.18)$$

or, for a mole

$$E_{\text{avg}} = 3RT \quad (2.19)$$

Hence,

$$C_v = (dE_{\text{avg}}/dT)_v = 3R \quad (2.20)$$

So that, for a solid, the heat capacity should be

$$C_v = 6 \text{ cal/deg-mol} \quad (2.21)$$

Table 2.1 shows examples of this.

It will be shown later that indium is used as a calibrator for differential scanning calorimetry (DSC).

The equation is called the *Petit–Dulong* equation.

2.4. THE EINSTEIN EQUATION

The foregoing holds in a classic sense, but the problem with it is that it predicts constancy. The data in the table fairly well substantiates the *Petit–Dulong* equation, but at lower temperatures, the heat capacities begin to drop.

If one is dealing with systems for which one assumes constant enthalpies in a temperature range, it is possible to commit errors, and it becomes important to obtain an idea of at which temperature (Φ_e , the so-called Einstein temperature), deviations may start to occur.

Table 2.1 Heat Capacities at 25°C

Compound	Heat capacity cal/°-g	Molecular weight	Heat capacity cal/°mol
Ca	0.156	40.08	6.25
Cu	0.092	63.54	5.85
In	0.056	114.82	6.43
Mg	0.243	24.31	5.90
Co	0.109	58.93	6.42

In this type of development, the quantum mechanical concept that the energy takes on values only as integers of one another, is used. The energy, for a harmonic oscillator is given by

$$E = nh\nu = n(h/2\pi)(\nu 2\pi) = n\hbar\omega \quad (2.22)$$

where h is Planck's constant (6.624×10^{-27} erg-s); ν is frequency; h (i.e., $h/2\pi$) is the modified Planck's constant (1.054×10^{-27}); and ω is the angular frequency; n is denoted the quantum number, and is an integer.

In an ensemble of N molecules, there will be various energy levels, E_1 (with $n = 1$), E_2 (with $n = 2$), and so on. The fraction (f_n) of the molecules in energy state n is given by the Boltzmann distribution, i.e.,

$$f_n = e^{-E_n/kT} \quad (2.23)$$

Hence, the total number of molecules is given by

$$N \sum e^{-E_n/kT} \quad (2.24)$$

The energy of all the molecules is given by

$$N \sum E_n e^{-E_n/kT} \quad (2.25)$$

By introducing Eq. (2.20), the average energy may now be calculated as

$$\begin{aligned} E_{\text{avg}} &= \sum E_n e^{-E_n/kT} / \sum e^{-E_n/kT} \\ &= \sum n\hbar\omega e^{-E_n/kT} / \sum e^{-E_n/kT} \end{aligned} \quad (2.26)$$

Introducing Eq. (2.19)

$$-E_n/RT = -\hbar\omega/RT = x \quad (2.27)$$

we may write Eq. (2.24) as

$$E_{\text{avg}} = \hbar\omega \sum ne^x / \sum e^x = (e^x + 2e^x + \dots)/(1 + e^x + e^{2x} + \dots) \quad (2.28)$$

If we use the notation

$$Y = (1 + e^x + e^{2x} + \dots) \quad (2.29)$$

then

$$dY/dx = (e^x + 2e^x + \dots) \quad (2.30)$$

so that, in Eq. (2.28)

$$E_{\text{avg}} = \hbar\omega d \ln Y / dx \quad (2.31)$$

Y [see Eq. (2.29)] is a geometric series with factor e^x , so that the sum is

$$Y = 1/(1 - e^x) \quad (2.32)$$

Hence,

$$E_{\text{avg}} = \hbar\omega / \{(\exp(\hbar\omega/kT) - 1)\} \quad (2.33)$$

This should be applicable at all temperatures, but at high temperatures

$$(\exp(\hbar\omega/kT) - 1 \approx 1 + (\hbar\omega/kT) + \dots - 1 = (\hbar\omega/kT) \quad (2.34)$$

so that

$$E_{\text{avg}} = \hbar\omega/(\hbar\omega/kT) = kT \quad (2.35)$$

that is, at temperatures higher than a given temperature Φ_E (the so-called Einstein temperature), the energy equals the classic energy.

The Einstein model gives profiles in reasonable agreement with experimental data, provided a suitable choice is made of the fundamental oscillator frequency. Both the terms $\hbar\omega$ and kT are energy terms, and it is more convenient to talk about temperatures than about frequencies, so it is conventional to tie this in with the Einstein temperature by:

$$\hbar\omega = k\Phi_E \quad (2.36)$$

With this terminology, Eq. (2.31) becomes

$$E_{\text{avg}} = k\Phi_E / \{\exp(\Phi_E/T) - 1\} \quad (2.37)$$

so that the heat capacity becomes

$$LdE/dT = Lk(\Phi_E/T)^2 \{\exp(\Phi_E/T)\} / \{\exp(\Phi_E/T) - 1\}^2 \quad (2.38)$$

where L is Avogadro's number. With experimental data, it is possible now to find (by iteration) a value of Φ_E that makes the data fit the best. Figure 2.8 is an example of this.

The severe assumption in the Einstein model is that there is only *one* fundamental frequency. (There should at least be three, one for each degree of freedom.) Debye later refined the model to include many frequencies and obtained an even better fit.

The important lesson to draw from this is that *heat capacities are (depending on the compound) at times sufficiently temperature-dependent and that this should be taken into account.*

The most common approximation is that

$$\Delta H = Q + qT \quad (2.39)$$

For instance, *International Critical Tables* uses this, and higher polynomial approximations, when tabulating heat capacities and enthalpies as a function of temperature.

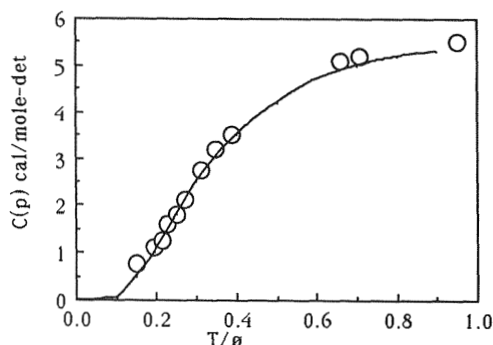


Fig. 2.8 Diamond heat capacities compared with the Einstein model with a Φ_e of 1320 K.

2.5. VAPOR PRESSURE

Both liquids and solids have vapor pressures. Vapor pressures of solids may be quite low, although some pharmaceutical substances (nitroglycerin, ibuprofen) have significant vapor pressures at room temperature.

Vapor pressure of a solid is measured by means of a so-called Knudsen cell, which measures the escaping tendency of the gas through a capillary.

For less precise, but more easily attainable vapor pressures, thermal gravimetric analysis (TGA) is employed. A covered pan with a pinhole is allowed to stay at a given temperature in the TGA, and the loss rate (dW_x/dt) is measured. This loss rate is proportional to the vapor pressure in the pan. A substance with known vapor pressure P_c (e.g., benzoic acid) is run in parallel, and the vapor pressure of the solid (P_x) is

$$P_x = P_b(dW_x/dt)/(dW_c/dt) \quad (2.40)$$

The development to follow holds for any condensed phase of a one-component system. It will be assumed that the equilibrium is between a solid and its vapor.

Gibbs' phase rule states that

$$df = C - P + 2 \quad (2.41)$$

where C is number of components, P is number of phases, and df is the degrees of phases. For a one-component system this becomes

$$df' = -P + 2 \quad (2.42)$$

In equilibrium the two phases have the same chemical potential, that is,

$$\mu_g = \mu_s \quad (2.43)$$

where the subscript g denotes gas and s denotes solid. The phase rule states that in the described situation there will be two degrees of freedom (e.g., temperature and pressure) that may be changed, so that at equilibrium, the following must hold:

$$\{d\mu_g/dT\}_p + \{d\mu_g/dp\}_T = \{d\mu_s/dT\}_p + \{d\mu_s/dp\}_T \quad (2.44)$$

It is recalled that

$$dG = -SdT + Vdp \quad (2.45)$$

and that μ is the G function per mole, so that

$$\{d\mu_g/dT\}_p = -s_s \quad (2.46)$$

and

$$\{d\mu_g/dp\}_T = -v_l \quad (2.47)$$

where s and v are molar entropy and volume. A similar set of equations for the solid phase. Hence, Eq. (3.2) may be written

$$-s_gdT + v_gdp = -s_sdT + v_sdp \quad (2.48)$$

or

$$(s_g - s_s)dT = (v_g - v_s)dp \quad (2.49)$$

or

$$dp/dT = (s_g - s_s)/(v_g - v_s) \quad (2.50)$$

$$(s_g - s_s) = \Delta H/T \quad (2.51)$$

where ΔH is the heat absorbed at constant temperature and pressure when 1 mol of substance passes from the solid to the gaseous state (i.e., it is the molar heat of sublimation). Regarding the volumes, the molar volume in the solid state is negligible compared with that in the gas phase, and if this is considered ideal, then

$$(v_l - v_s) \approx v_l = RT/P \quad (2.52)$$

Introduction of Eqs. (2.51) and (2.52) into Eq. (2.50) gives:

$$dp/dT = (\Delta H/T)/(RT/p) \quad (2.53)$$

or

$$dp/p = \Delta H/(RT^2) \quad (2.54)$$

This integrates to

$$\ln[p] = -\Delta H/(RT) + \beta \quad (2.55)$$

where β is an integration constant.

An example of this is the vapor pressure of benzoic acid, given in Table 2.2.

The direct data are plotted in Fig. 2.9 and the logarithmic transformation is plotted in Fig. 2.10.

It is noted that the heat of vaporization is

$$\Delta H = 1.99 \times 7.685 = 15.4 \text{ kcal/mol}$$

It may also be noted that it is assumed that the enthalpy of vaporization is not temperature-dependent, and (from the source) it is not so in the temperature interval shown.

2.6. MELTING POINTS

If a substance is at a temperature sufficiently high for it to be in a melted condition, its vapor pressure curve will follow the Clausius Clapeyron equation, except that now the slope is ΔH_{vap} (i.e., the heat of vaporization).

Table 2.2 Vapor Pressure of Benzoic Acid as a Function of Temperature

Temp (°C)	$P = \text{vapor pressure}$ (mmHg)	$1000/T \text{ K}^{-1}$	$\ln[P]$
60	0.1065	3.002	-2.244
70	0.2085	2.914	-1.568
80	0.3928	2.832	-0.934
90	0.7147	2.754	-0.336
100	1.2592	2.680	0.230
110	2.1539	2.610	0.767

Source: West and Selby (1967).

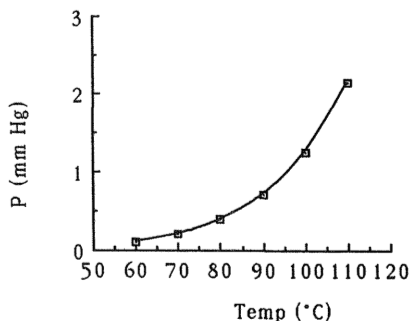


Fig. 2.9 Vapor pressure of benzoic acid as a function of temperature.

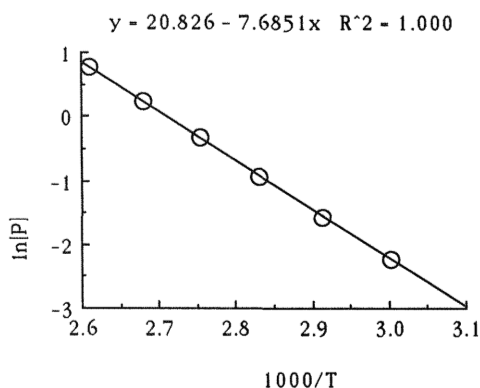


Fig. 2.10 Data in Table 2.2 (see Fig. 2.9) treated according to Eq. (2.55).

The heat of fusion ΔH_{melt} is the difference between the two, that is,

$$\Delta H_{\text{sub}} - \Delta H_{\text{vap}} = \Delta H_{\text{melt}} \quad (2.56)$$

Vapor pressure curves (Fig. 2.11) and melting points will assume a special significance when further discussion on polymorphism is presented.

2.7. POLYMORPHISM

Polymorphism is the phenomenon of a chemical entity being able to exist in two different crystal forms. It will be discussed in greater detail elsewhere in this text, but a few points and examples are appropriate to mention at this point.

Ceolin et al. (1997), have reported on p , T diagrams of carbamazepine. Carbamazepine (*USP*) is monoclinic, but other polymorphic forms exist. Sublimation gives a triclinic polymorph, but single crystals are difficult to produce in this manner. The authors produced a crystal of dimensions $10 \times 70 \times 430 \mu\text{m}$ that they used for single-crystal characterization of the polymorph.

They show the following topological p , T diagram (Fig. 2.12).

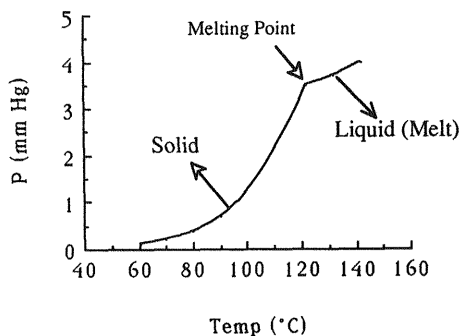


Fig. 2.11 Vapor pressure diagram of benzoic acid (melting point 122°C).

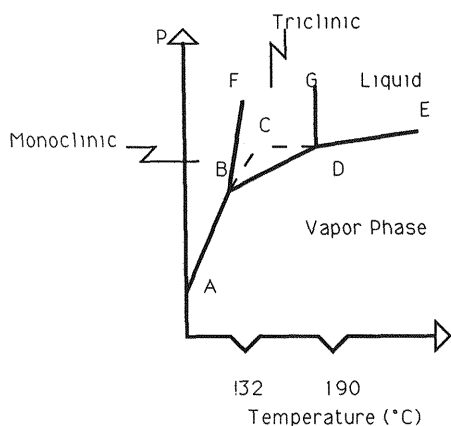


Fig. 2.12 The literature caption (the reference Fig. 4) should read: B is the triple point between triclinic, monoclinic and vapor; D is the triple point between triclinic, liquid, and vapor. (Data from Ceolin et al., 1977.)

They found the transition point by using a tube heated at the position of the solid, and by monitoring the deposit and the temperature along the tube; they found that 132 was the triple point.

REFERENCES

- Ceolin R, Toscanini S, Gardette M.-F, Agafonov VN, Dzyabchenko AV, Bachet B (1997). *J Pharm Sci* 86:1062.
- Einstein A (1907). *Ann Physik* 22:180.
- Grant DJW, York P (1986). *Int J Pharm* 30:161.
- Hersey JA, Krycer I (1981). *Int J Pharm Technol Prod Manuf* 2(2):55.
- Hiestand E (1997). *J Pharm Sci* 86:987.
- Hüttenrauch R (1983). *Pharm Ind* 45(4):435.
- Hüttenrauch R, Keiner I (1979a). *Int J Pharm* 2:59.
- Hüttenrauch R, Keiner I (1979b). *Powder Technol* 22:289.

- Jozwiakowski MJ, Nguyen NT, Sisco JJ, Spankac CW (1996). *J Pharm Sci* 87:193.
- Longuemard P, Jbilou M, Guyot-Hermann A-M, Guyot J-C (1998). *Int J Pharm* 170:51.
- Moriata M, Nakai Y, Kukuoka E, Nakajima SI (1984). *Chem Pharm Bull* 32:4076.
- Musa MN (1972). PhD dissertation, University of Wisconsin, Madison, WI, p 79.
- Pick H, Weber H (1950). *Z Phys* 238:409.
- Vachon MG, Grant DJW (1987). *Int J Pharm* 40:1.
- Weast RC, Selby SM (1967). *Handbook of Chemistry and Physics*, 48th ed. The Chemical Rubber Co., Cleveland, OH, p. D141. 143.

3

Solubility

3.1. Equilibrium Solubility	28
3.2. Heat of Solution	28
3.3. Solubility Determination: Effect of Temperature	32
3.4. Effect of Electrolytes on Solubility	37
3.5. Mixed Solvent Systems	37
3.6. Effect of Dielectric Constant on Solubility Parameters	38
3.7. Multiple Solubility Peaks	39
3.8. Complexation	41
3.9. Cyclodextrins	42
3.10. Solubility and pH	42
3.11. Prediction Equations for Solubility in Binary Solvents	44
3.12. Solubility in Micellar Systems	44
3.13. Solubility of Poorly Stable Compounds	45
3.14. Effect of Surfactants	46
3.15. Effect of Particle Size	46
Symbols	46
References	47

Solubility of compounds is of great importance in pharmaceuticals, and the subject has been subdivided into the foregoing subtopics.

3.1. EQUILIBRIUM SOLUBILITY

Whenever the term *solubility* is employed, it is tacitly assumed that it is equilibrium solubility. In other words, it assumes that *a (stable) solid (the solute) is placed in contact with a liquid (the solvent), and the system is allowed to be agitated for a long while, or by other means allowed to reach a state of equilibrium, characterized by the fact that the concentration of solute has reached a constant level.*

This definition is by no means easy to establish in practice. Such things as small temperature fluctuations, and that solubility may be a function of particle size, makes the experimental establishment of solubility of a compound difficult to achieve. Add to that the fact that solids of higher energetics (metastable polymorphs or amorphates) have higher apparent solubilities also confounds the issue. At times (e.g., in the case of benzodiazepam), the drug substance, as first produced (in clinical trials), turned out to be a metastable polymorph. Apparent equilibrium solubilities were established and were thought to be true equilibrium solubilities because the figures were reproducible, until one day the more stable form happened to be produced, and this had a lower solubility. Because it is never really certain that any drug substance produced is *actually* the stable polymorph, the term *equilibrium solubility* is clouded to some degree with uncertainty. In this chapter to follow it is going to be assumed that solubility is exactly what the foregoing italicized definition purports it to be.

For the purposes of this book, there are four types of equilibrium situations (Hill, 1933) that may be considered:

1. The solid phase is a pure compound, and there is one liquid phase.
2. The solid phase is a pure compound, and there is more than one liquid phase.
3. The two components form a solid solution in such a way that there is unlimited solubility in the solid phase.
4. There are two solid solutions forming (i.e., there is limited solubility in the solid phase).

Of these, case 1 is overwhelmingly the most common situation. Case 2 is at times important in differential scanning calorimetry (DSC) work. If the melts of compound A and compound B are immiscible, then the DSC thermogram will show two peaks, one at each compound's melting point, otherwise one broad peak will occur. This will be discussed in a later chapter.

3.2. HEAT OF SOLUTION

When a substance (the solute) dissolves in a solvent there are certain changes that occur. Some solutions are ideal solutions, and in such solutions the volumes, for instance, are additive.

A property that is of importance in the following is the heat associated with the solution of a solid drug substance in a solvent (most often water), and it will become apparent that the effect of temperature on solubility is associated with an aspect of this thermal phenomenon.

There is a fair amount of misinterpretation of the "heats of solution" in literature, and in this aspect it is fruitful to quote a *very old*, but comprehensive

reference (Taylor, 1931). If the solubility of a compound in a solvent is plotted versus temperature then, in its simplest form, the curve will either rise or fall. If heat is evolved *when the solid is dissolved in an (almost) saturated solution*, then the solubility of the compound will decrease with increasing temperature, and the opposite, in the simple case, is also true. However, to quote Taylor (1931):

[I]t is common knowledge that when water is poured upon solid potassium hydroxide, much heat is evolved; if one deduced therefrom that the solubility of the compound decreased with the temperature, the error would be flagrant. The initial heat of solution is positive; it may be that the total heat of solution is positive, but the final heat of solution, representing the dissolving of the last increment entering the solution at the saturation point, is negative, and hence a rise of temperature will result in the dissolving of another increment.

The relations between partial molar and integral heats of solutions are described by Brønsted (1943a), in the following words, directly translated (the word *thermodynamic function* used for the term A in the translation):

To visualize the connection one may utilize a graphic presentation in which one most advantageously utilizes the x -concentration scale and in place of A which applies to $n_1 + n_2$ molecules of mixture [utilizes] A_i , the integral mixing [thermodynamic] function for one mole of mixture. The equation corresponding to this may be derived in direct analogy with the [previously cited equations] containing $n_1 + n_2$ moles but may also be obtained by introducing:

$$A = (n_1 + n_2)A_1$$

and

$$x = n_1/(n_1 + n_2)$$

One, hence, obtains the following equation, valid at constant temperature and pressure:

$$A_i = xA_1 + (1 - x)A_2 \quad (17)$$

$$\partial A_i / \partial x = A_1 - A_2 \quad (18)$$

$$A_1 = A_i + [(1 - x)^{\partial A_i} / \partial x] \quad (19)$$

$$A_2 = A_i - x \partial A_i / \partial x \quad (20)$$

as well as the relation between the differential [thermodynamic functions]

$$x(\partial A_1 / \partial x) + (1 - x)(\partial A_2 / \partial x) = 0 \quad (21)$$

The connection between A_1 , A_2 , and A_i is shown in Fig. 2 [reconstructed as Fig. 3.1 in this text].

At a further point in the text Brønsted (1943b) states that A the thermodynamic function "can be the S , V , E , F , G , or H functions."

The foregoing text talks to the difference between differential heats of solution and integral heats of solution; examplewise the heat evolved per mole of sulfuric acid added to 1 mol of water. The heat of solution (H) of a mixture of n_1 moles of a compound A in n_2 moles of a solvent B is given by:

Table 3.1 Water and Sulfuric Acid. Heat of Solution as a Function of Composition

Mole fraction acid (X)	$1000 \times$ heat evolved per mole of acid	ΔH per mole of solution
0	0	0
0.1	15.6	-1.56
0.2	12.94	-2.59
0.3	10.71	-3.21
0.35	9.65	-3.38
0.4	8.63	-3.452
0.45	7.68	-3.456
0.5	6.73	-3.37
0.55	5.81	-3.20
0.6	4.87	-2.93
0.65	4.06	-2.64
0.7	3.2	-2.30
0.75	2.6	-1.95
0.8	1.97	-1.58
0.85	1.42	-1.21
0.9	0.93	-0.84
0.95	0.45	-0.43
1.00	0	0

Source: Data from Brønsted, 1909; Marshall, 1933.

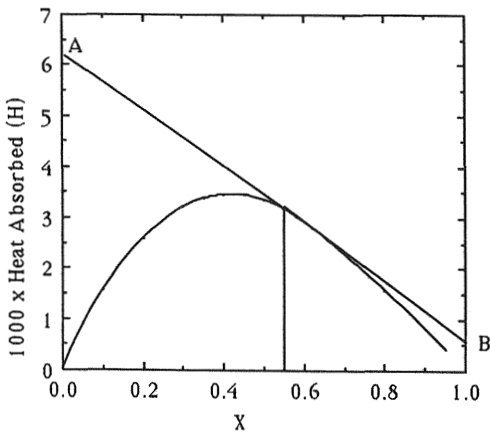


Fig. 3.2 Heats of solution of the sulfuric acid system: The abscissa is the mole fraction of sulfuric acid.

Fig. 3.3. It is noted that in Fig. 3.3 the heats of solution are terminated by the solubility X .

The foregoing statements may (incorrectly) imply that there is either an increase or a decrease in solubility of a compound with temperature. There are many exceptions. Ammonium nitrate solubility in water, for instance, exhibits breaks at 32°C, 83°C, and 126°C. Maxima and minima in solubility/temperature curves also occur, and some of the situations of this will be discussed later in this chapter.

3.3. SOLUBILITY DETERMINATION: EFFECT OF TEMPERATURE

The subject of eutectic diagrams will be taken up in a later chapter, but a short outline will be given at this point.

The simple solution situation referred to in Sec. 3.1 exhibits a eutectic diagram such as shown in Fig. 3.4a. The so-called liquidous line in the right part of the eutectic, QU, is a compositional line where, at a given temperature, T , there is an equilibrium between solid solute B and a solution of B in water of composition x . This, in essence, is a solubility curve, and if the axes are flipped, as shown in Fig. 3.4b, then a conventional representation of solubility versus temperature results.

Solubility of solids are determined by placing an excess of solid in contact with the solvent in a hermetic containers (ampoule or closed test tube) and agitating it in a constant temperature bath. It is conventional to use 72 h for equilibration.

If less time is used, then the solubility may be obtained by iterative extrapolation, as demonstrated in Table 3.2. Samples are taken after certain times (here multiples of 12 h), and the supernatant is assayed. The concentrations are then plotted as a function of time, as shown in Fig. 3.5. It is seen that the data "seem" to level off at 59, so the solubilities are subtracted from 59 (see column 3 in Table 3.2), and the logarithm taken of these numbers. These are plotted in Fig. 3.6. The process may be

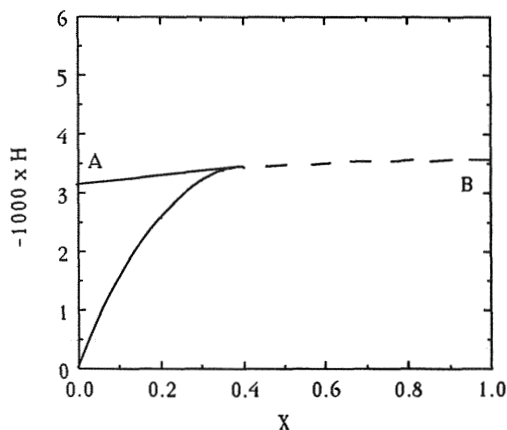


Fig. 3.3 Heats of solutions depicted in Fig. 3.1 but terminated by the solubility X , representing the highest concentration.

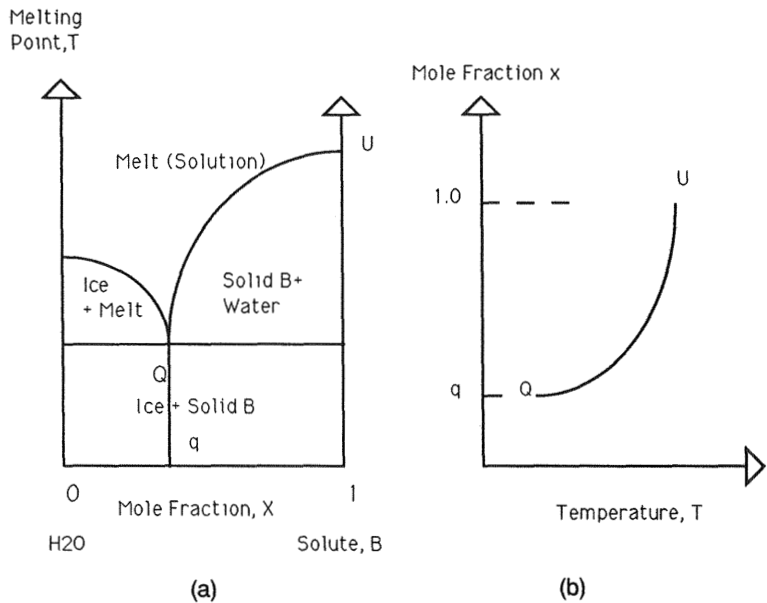


Fig. 3.4 (a) Eutectic diagram of water and a solute, B. (b) The right side of the eutectic diagram from Fig. 3.4a plotted with reversed axes (i.e., solubility as a function of temperature).

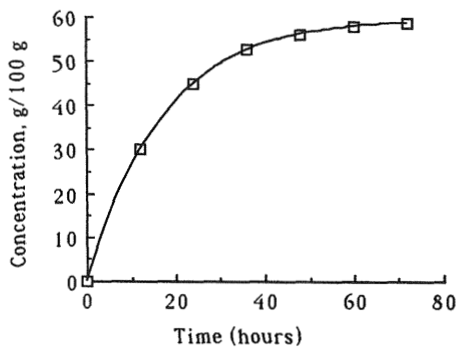


Fig. 3.5 Data from Table 3.2.

Table 3.2 Example of Solubility Determination by Iterative Extrapolation

Time (h)	Solubility (g/1000 g)	59 – S	ln[59 – 2]
0	0	59	4.078
12	30	29	3.367
24	45	14	2.639
36	52.5	6.5	1.872
48	56	3	1.099
60	57.8	1.2	0.18

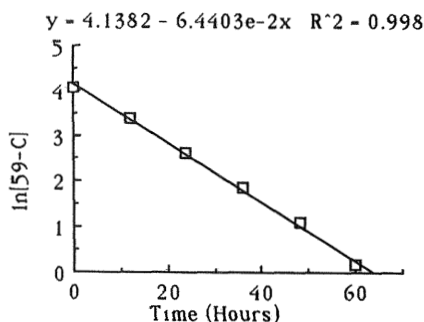


Fig. 3.6 Data from Fig. 3.4 treated by iteration.

repeated with a figure different from 59. The value of the iterant that gives the best fit (the least sum of residual squares) is then assigned as the solubility.

Solubility is best expressed as molality or as weight of solute per gram of solvent (i.e., not per cubic centimeter of solution). The conventional treatment of solubility as a function of temperature is to note that the chemical potential of a compound in solution, at a concentration level corresponding to an activity of a , is given by

$$\mu_1 = \mu^0 + RT \ln a \quad (3.4)$$

Here, μ^0 is a reference state, and obviously is the chemical potential when the activity is unity (i.e., when $a = 1$ molal).

When there is equilibrium between a solid and a saturated solution (of activity a_s), then the chemical potential of the solid μ_s , equals that of the compound in solution, given by Eq. (3.4), that is,

$$\mu_s = \mu^0 + RT \ln a_s \quad (3.5)$$

Dividing through by T and differentiating relative to T now gives

$$\{\partial(\mu_s/T)/\partial T\}_p dT = \{\partial(\mu^0/T)/\partial T\}_p dT + R d(\ln a_s) \quad (3.6)$$

It is recalled that

$$\{\partial(\mu/T)/\partial T\}_p = -h/T^2 \quad (3.7)$$

This when inserted in Eq. (3.6) then gives (after rearrangement)

$$-\{(h_s - h^0)/T^2\} dT = R d(\ln[a_s]) \quad (3.8)$$

$h^0 - h_s = -(h_s - h^0)$ is the enthalpy associated with transferring 1 mol of solid into a large quantity of saturated solution and $h^0 - h_s$ is commonly simply denoted ΔH . Denbigh (1961) defines h_s as "the partial molar enthalpy of the component in the ideal solution" and ΔH would, therefore, at a given temperature, be the partial molar enthalpy plus a constant (h^0)

$$R d(\ln[a_s])/dT = \Delta H/T^2 \quad (3.9)$$

This integrates to

$$\ln[a_s] = -\{\Delta H/(RT)\} + \beta \quad (3.10)$$

where β is an integration constant; a_s is the activity of the solute at saturation and is given by

$$a_s = \gamma_s S \quad (3.11)$$

where S is the saturation concentration (in molality) and γ_s is the activity coefficient at saturation. If this is assumed to be unity, then Eq. (3.10) becomes the well-known, and often used equation

$$\ln[S] = -\{\Delta H/(RT)\} + \beta \quad (3.12)$$

This is referred to as a Van't Hoff plot (although this latter, properly, is associated with equilibrium constants, not solubilities). More correctly Eq. (3.12) should be written:

$$\ln[S] = -\{\Delta H/(RT)\} + \beta - \ln[\gamma_s] \quad (3.14)$$

If γ_s is temperature-independent, then the logarithm of the saturation concentration is linear in reciprocal absolute temperature, a plotting mode that is often used. An example of this is shown in Table 3.3 and Fig. 3.7.

Linearity of the Van't Hoff plot assumes (a) that ΔH is independent, and (b) that the activity coefficient (γ_s) is temperature-independent. If they are not, then the Van't Hoff plot will not be linear. An example of this is shown in Fig. 3.8.

Grant et al. (1984) hypothesized that if, rather than "the partial molar enthalpy of solution of the solute, ΔH_2^* , is independent of temperature, we assume that it is a linear function of temperature, as follows: $\Delta H_2^* = a + bT$." They interpret that " a may be considered to be the *hypothetical* value of ΔH_2^* at the absolute zero of temperature and b is the change in the apparent partial molar heat capacity of the solute at constant pressure, ΔC_{p2}^* , which is itself assumed to be independent of temperature. There is evidence that the introduction of terms containing higher powers of T , e.g., cT^2 , etc., is unnecessary." If the curvature in Fig. 3.4 is caused by the heat of solution not being temperature-independent, i.e.,

$$\Delta H = AT + B \quad (3.15)$$

where A and B are constants, then,

$$d \ln S/dT = \Delta H/(RT^2) \quad (3.16)$$

Combining this with Eq. (3.15) then gives

$$T d \ln S/dT = \{A/(RT)\} + (B/R) \quad (3.17)$$

Table 3.3 Solubility of Orthorhombic Sulfanilamide in Ethanol

Temp (°C)	Solubility (g/1000 g)	$\ln[S]$	$1000/T(K^{-1})$
47.4	28.22	3.34	3112
40.3	23.34	3.15	3.19
29.6	16.78	2.82	3.30
24.1	14.15	2.65	3.36

Source: Data from Milosovich, 1964.

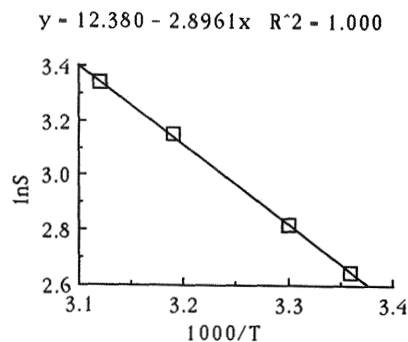


Fig. 3.7 Data in Table 3.3 plotted according to Eq. (3.12).

Equation (3.17) integrates to

$$\ln S = -A/T + B \ln T + \beta \quad (3.18)$$

This may be fitted by nonlinear programs, but for these to work, one must have a good estimate of A and B . To obtain good estimates, most graphing programs will calculate $(d \ln S_s)$ which may then be multiplied by T and plotted by way of Eq. (3.17) versus $1/T$. This should produce a straight line with intercept B/R and slope A/R (Fig. 3.9).

A and B may now be estimated from the slope and intercept of this line, *and may be used as first approximations in a nonlinear program*. This approach has been employed by several recent investigators (Pudipeddi, 1998; Jozwiakowski et al., 1996).

It should, again, be emphasized that the enthalpy term in both Eqs. (3.12) and (3.18) corresponds to “the partial molar enthalpy of the component in the . . . solution . . . [i.e.] the heat absorbed, at constant temperature and pressure, when 1 mole of the component dissolves in the . . . solution.” (Denbigh, 1961). *This fact, in itself, makes it quite understandable why the Van’t Hoff can not be expected to be linear.*

Consider the diagram in Fig. 3.1. Suppose the depicted compound at a temperature of T_1 had a solubility corresponding to Q and at a higher temperature had a

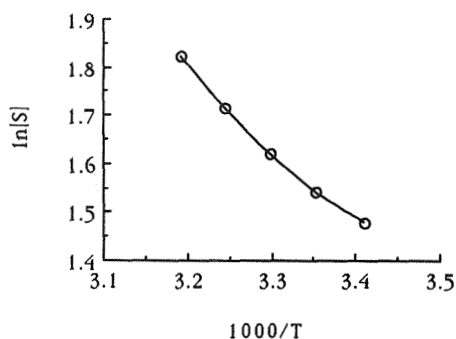


Fig. 3.8 Solubility of d_1 - p [pseudoephedrine]. (Data from Pudipeddi, 1996.)

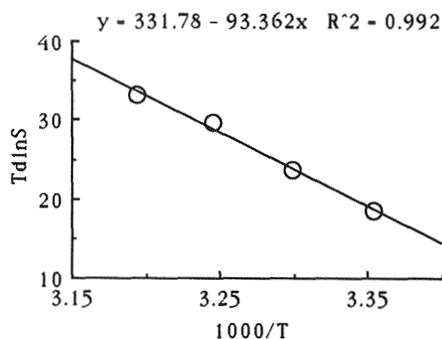


Fig. 3.9 Derivative curve ($d \ln S$) of data in Fig. 3.8 versus T^{-2} .

solubility corresponding to L , then *the differential enthalpies of solutions would be a function of temperature*; hence, it is not unexpected that the Van't Hoff plot is not linear, but it is rather to be expected. To assign the change in heat capacity as an explanation to the nonlinearity is rational only in the sense that the composition changes with temperature; hence, the change in heat capacity also changes.

There are many examples of this; for instance, Longuemard et al. (1998) have reported on the solubility of aspirin in 38% alcohol; they failed to obtain linearity according to the Van't Hoff, although in this case the curvature may be because the ordinate is in grams per liter (g/L), rather than in grams per 1000 g (g/1000 g) of solvent.

3.4. EFFECT OF ELECTROLYTES ON SOLUBILITY

The solvent has a great influence on solubility and should always be specified. In aqueous solutions, the concentration of electrolytes may greatly affect the solubility of a compound. (It will be seen later, that this is particularly true for a compound that is, itself, an electrolyte). Figure 3.10 shows the effect of sodium chloride concentration on the solubility of a bisnaphthalimide derivative.

3.5. MIXED SOLVENT SYSTEMS

The use of mixed solvent systems is often necessary in pharmaceuticals when a drug is poorly soluble. Cosolvents used are

- Ethanol
- Propylene glycol
- Glycerin
- Polyoxyethylene glycols

Ternary diagrams are used to visualize where maximum solubility occurs when more than one solvent is used (Fig. 3.11).

The length of PA is the percentage of water, the length WB is the amount of ethanol and, here, EC is the percentage of glycerol. The lines in this presentation mode are parallel to the sides in the triangle. In a different presentation mode they

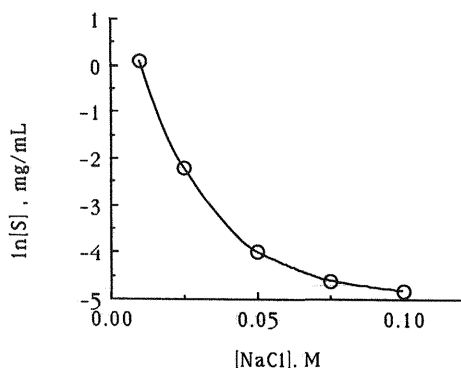


Fig. 3.10 Effect of salt concentration on the solubility of a bisnaphthalimide. (Data from Raghavan et al., 1996.)

are cast perpendicularly to the axes. A point inside the triangle, such as D, defines one given composition.

If solubilities are determined for many solvent compositions, then the solubility would be the same (10 mg/g, 20 mg/g, etc.) for given compositions of the solvent, and such points can be connected to form isotherms and diagrams, such as Fig. 3.12, would result. The figure to the left in Fig. 3.12 implies a maximum solubility, whereas in the other diagram, the more of one cosolvent that is added, the larger the solubility is.

3.6. EFFECT OF DIELECTRIC CONSTANT ON SOLUBILITY PARAMETERS

Frequently the solubility is a function of the dielectric constant of the medium. Often, the relation is that of the Jaffe equation:

$$\ln[S] = (A/\epsilon) + B \quad (3.19)$$

where A and B are constants and ϵ is the dielectric constant of the solvent. An example of this is shown in Table 3.4, in which the solubility of a compound is tabulated as a function of the dielectric constant of the medium (glycerin/water

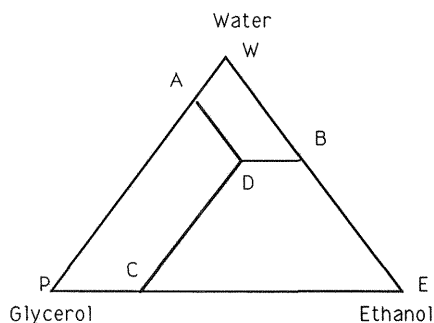


Fig. 3.11 Ternary diagram.

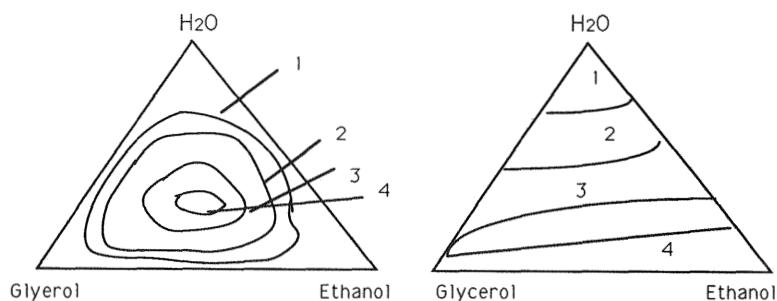


Fig. 3.12 Ternary diagrams of the two types of solubility.

mixtures). Most often, with hydrophobic drugs the solubility decreases with increasing dielectric constant. The opposite happens at times, and an example of this is shown in Table 3.4 and Fig. 3.13.

It is particularly useful, from a practical point of view, to carry out solubilities in solvent pairs of different ratios to vary the dielectric constant. Graphs will often be linear when plotted as in Fig. 3.13, but they will often show maximum solubility at a given dielectric constant (Fig. 3.14), and the practical part of this is that once this is established, almost any other solvent pair will show maximum stability at that dielectric constant.

Rather than using dielectric constant as a measure, the Hildebrand solubility parameter δ is often employed. Shinoda (1978) defines this as

$$\delta = \{(\Delta H_v - RT)/V\}^{1/2} \quad (3.20)$$

where ΔH_v is the heat of vaporization of the solvent, V its molar volume, and R the gas constant.

Figure 3.15 gives an example both of plotting the solubility of a compound (caffeine) in solvent mixtures with different solubility parameters, the plotting as a function of their dielectric constant.

3.7. MULTIPLE SOLUBILITY PEAKS

Solubility profiles vis-a-vis the solubility parameter of the solvent at times shows multiple peaks. This is the so-called chameleonic effect (Sunwoo and Eisen, 1971;

Table 3.4 Effect of Dielectric Constant on Solubility of Bisnaphthalimide

Dielectric constant	Solubility (S , mg/mL)	$\ln[S]$	100/ DE
78.5	2.49	0.912	1.274
74.9	2.30	0.833	1.335
65.9	2.00	0.693	1.517
52.6	1.42	0.351	1.900
45.45	1.09	0.086	2.200
42.5	0.98	-0.02	4.333

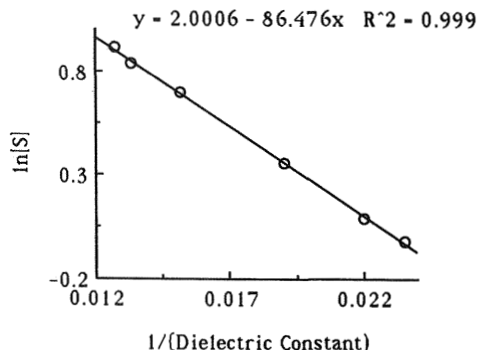


Fig. 3.13 Effect of dielectric constant on the solubility of bisnaphthalamide. (Data from Raghavan et al., 1996.)

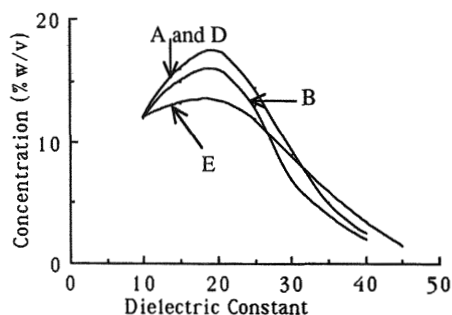


Fig. 3.14 Effect of dielectric constant on the solubility of phenobarbital in four systems: A, propylene glycol:ethanol; B, glycerin:ethanol; C, water:ethanol; D, propylene glycol:water. (Data from Lordi et al., 1964.)

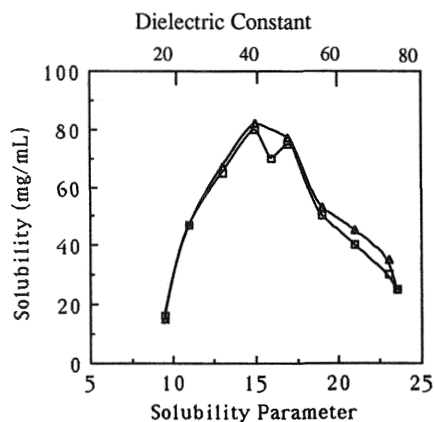


Fig. 3.15 The solubility of caffeine in a solvent consisting of dioxane and water at 25°C: Top curve (with top abscissa) is solubility versus dielectric constant, and the lower curve (with the lower abscissa) is the solubility versus the solubility parameter (δ_1). (Data from Martin et al., 1961.)

Escalera et al., 1994; Bustamante et al., 1994; Romero et al., 1996); it also exists for polymers (Hoy, 1970), and the molecules appear to adjust their solubility to fit the solvent polarity (Martin et al., 1985). Systems of this type are often characterized by nonspecific van der Waals forces as well as strong specific interactions, so that the Hildebrand solubility parameters no longer can explain the solubility of, for instance, polar solutes in semipolar (or polar) solvents (Jouyban–Gharamaleki and Acree, 1998).

3.8. COMPLEXATION

Drug substances may complex with complexing agents. An example is ascorbic acid/niacinamide (niacinamide ascorbate). In general, one of the two components of the system (e.g., drug A), is called the substrate and the other B, is called the ligand.

Complexation is often applicable to solubility problems in pharmaceuticals. A drug A (the substrate) will react with another compound B (the ligand) and form a weak equilibrium.



The equilibrium constant of this (the stability constant) is

$$K = [AB]/[A][B] \quad (3.21)$$

The concentration of uncomplexed substrate is the solubility when no ligand is present.

$$[A] = S \quad (3.22)$$

The quantities in brackets are actual concentrations in the complexed system. If, by unbracketed B, we denote the concentration of ligand calculated based on the amount added, then {B} will be this amount less the amount complexed.

$$[B] = B - [AB] \quad (3.23)$$

The measured solubility S_{obs} is the solubility S plus the amount complexed.

$$S_{\text{obs}} = S + [AB] \quad (3.24)$$

so

$$[AB] = S_{\text{obs}} - S \quad (3.25)$$

and

$$[B] = B - S_{\text{obs}} - S \quad (3.26)$$

Inserting the expressions for [B] and [AB] in the equilibrium equation [see Eq. (3.21)] gives

$$K = (S_{\text{obs}} - S)/\{S(B - [AB])\} = (S_{\text{obs}} - S)/\{S(B - S_{\text{obs}}) - S\} \quad (3.27)$$

which rearranges to

$$S_{\text{obs}} - S = SKB/(1 + KS) \quad (3.28)$$

Hence by measuring the solubility as a function of the added ligand B (expressed as concentration), a straight line should ensue with a slope of β , given by

$$\text{Slope} = \beta = KB/(1 + KS) \quad (3.29)$$

When S is small, then the equation becomes, approximately

$$S = S_0 + KB \quad (3.30)$$

as demonstrated in Fig. 3.16.

The complexation equations have been examined extensively for 1:1 complexes (Higuchi and Connors, 1965; López et al., 1987; Ahmed et al., 1991). Complexation is useful in several applications of solids; for instance, ascorbic acid and niacinamide complexes. If the two compounds are placed, for example, in a soft-shell capsule, they will interact in time (and the complex is yellow). So in general they are pre-reacted by placing them in a mixer, adding alcohol, which allows the complex to form, and then drying the powder mass.

3.9. CYCLODEXTRINS

A special note on cyclodextrins is in order. These compounds (α , β , and γ depending on the size of the ring), form inclusion compounds with many drugs. They take up either the entire molecule or some hydrophobic portion of it into their "cavity." This affects many of the physicochemical properties of the complexed drug, without affecting pharmacological properties (Duchene and Wouessidjewe, 1996; Loftson and Brewster, 1996; Irie and Uekama, 1997; Rajewski and Stella, 1996). The problem may be considered in the opposite sense, and Loftson and Fridriksdottir (1998) have shown the effect of water-soluble polymers and of a series of drugs on the solubility of β -cyclodextrin in water (Figs. 3.17 and 3.18).

3.10. SOLUBILITY AND pH

The following considerations deal with the solubility of an acid as a function of pH, but the inverse problem of an amine and its solubility as a function of pH would follow the same lines. Mostly an acid is less soluble than its salts, and at low pH, the Henderson-Hasselbach equation will predict that

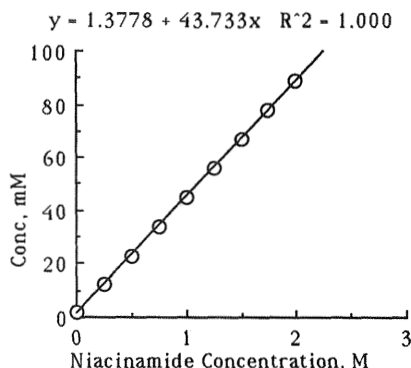


Fig. 3.16 Effect of a ligand (niacinamide) on the solubility of a bisnaphthalimide. (Data from Raghavan et al., 1996.)

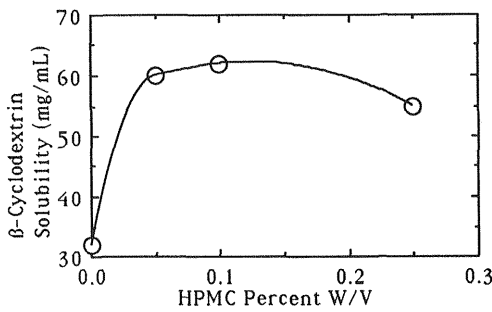


Fig. 3.17 Effect of HPMC on β -cyclodextrin solubility in solutions saturated in carbamazepine. (Data from Loftson and Fridriksdottir, 1998.)

$$\text{pH} = \text{pK} + \log_{10}[C_A/C_{HA}] = \text{pK} + \log_{10}[C_A/S_{HA}] \tag{3.31}$$

or

$$C_{HA} + C_A = C_{HA}\{1 + 10^{\text{pH}-\text{pK}}\} \tag{3.32}$$

where C_{HA} is the solubility of the acid form, C_A is the concentration of the acid anion, and pK is the pK of the acid. If the solubility of HA , denoted S_{HA} , is less than what is calculated from the solubility product of the metal counterion M ,

$$K_1 = [\text{M}^+][\text{A}^-] \tag{3.33}$$

then the solubility S is given by

$$S = S_{HA}\{1 + 10^{\text{pH}-\text{pK}}\} \tag{3.34}$$

In that case the solubility versus pH curve would have the appearance of a titration curve. At high pH , the limiting solubility would be given by Eq. (3.33).

If, for instance, the pH of an acid HA is increased by addition of an alkali MOH , then the amount in solution will increase by Eq. (3.32) until such a point that Eq. (3.33) is just satisfied. At this point, let us assume that p moles of MOH have been added, and that the pH is sufficiently high that the solubility is simply equal to the concentration of A^- , so that both $[\text{M}^+]$ and $[\text{A}^-]$ is equal to p ,

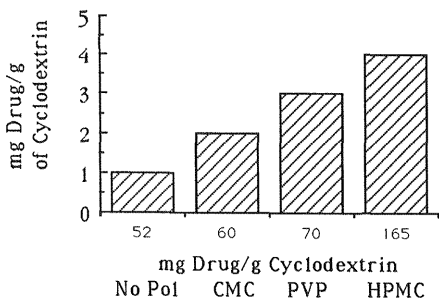


Fig. 3.18 The solubility of a hydrocortisone/ γ -cyclodextrin complex in aqueous solutions of 0.25 CMC, PVP, or 0.1% w/v HPMC. (Data from Loftson and Fridriksdottir, 1997.)

$$K = p^2 \quad (3.35)$$

If a bit more MOH is added, the concentration of each ion would be $p + \Delta$ where Δ is the small amount. But

$$\{p + \Delta\}^2 > P^2 = K \quad (3.36)$$

so that MA will precipitate out: a plateau would be reached.

If the acid is dibasic, then often, the solubility product of M_2A is smaller than that of MHA and in this case the solubility versus pH curve would decrease above the second pH of the compound.

3.11. PREDICTION EQUATIONS FOR SOLUBILITY IN BINARY SOLVENTS

There have been a series of attempts in literature (Martin et al., 1980; Yalkowsky and Roseman, 1981; Williams and Amidon, 1984; Ochsner et al., 1985; Acree et al., 1991; Acree, 1992, 1996; Barzegar-Jalali and Hanaee, 1994; Barzegar-Jalali and Jouyban-Gharamaleki, 1996) to establish a reliable predictor for an unexperienced solute solubility in binary mixtures of solvents with known neat properties. One of these is the Redlich-Kister (or, the CNIBS/R-K) equation.

Here X_m , the mole fraction of the solubility is related to f_a and f_b , the volume fractions of the two solvents A and B when no solute is present, where X_a and X_b denote the mole fraction solubility in the neat solvents A and B of the solute, and β_0 , β_1 , and β_2 are least-squares-fitted constants in the equation:

$$\ln[X_m] = f_a \ln[X_a] + f_b \ln[X_b] + F_a f_b \{S_0 + S_1(f_a - f_b) + S_1(f_a - f_b)^2\} \quad (3.37)$$

Jouyban-Garamaleki and Hanaee (1997) have investigated this equation for a series of hydroxybenzoic acid esters.

3.12. SOLUBILITY IN MICELLAR SYSTEMS

Although perhaps not strictly applicable to "solids," solubility in micellar systems is of importance. Often the important aspect of solubility is in dissolution testing, and a short note on the effect of micellar systems is of importance.

Micellar systems, in a certain way, are similar to two-phase systems with one big exception. For instance, whereas in oil in water systems the oil droplets are continents unto themselves, and the oil molecules in a droplet are fairly much the same independently of time, in micellar systems there is *an equilibrium* between monomers in solution, and molecules of the amphiphile in the micelle.

As far as solubility is concerned, there is a partition of solute molecules between solute in the aqueous phase and solutes in the micellar phase, so that in that aspect, the phenomenon is one of partition, *with the exception* that the linear increase in solubility of, for example, the drug, does not start taking place before the critical micelle concentration (CMC) is achieved. Solubility plots, therefore, have the appearance shown in Fig. 3.19.

Hammad and Müller (1998), for instance, has reported on the solubility of clonazepam in mixed micelles.

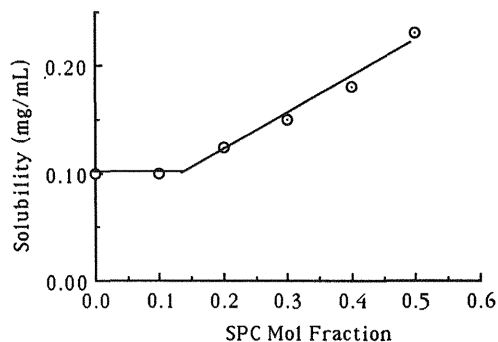


Fig. 3.19 Solubility of chlonazepam in soya phosphatidyl-choline. (Data from Hammad and Müller, 1998.)

Niacinamide is often used to increase solubility of drugs (Fawzi et al., 1980; Truelove et al., 1984; Malaviolle et al., 1987; Chen et al., 1994). For instance, Bogdanova et al. (1998) have shown that melts made with niacinamide and indomethacin give rise to a maximum solubility at an indomethacin concentration of about 7.5%.

3.13. SOLUBILITY OF POORLY STABLE COMPOUNDS

When a compound is poorly stable in aqueous solution, then the Nogami method may be particularly useful, because the longer the solubility experiment goes on, the more drug substance will degrade. Then, it is worthwhile selecting a smaller value for the sampling interval, q , for instance, 20 min.

The method of approaching this is as follows: the rate with which the compound goes into solution in V milliliters of liquid is given by:

$$dM/dt = -VdC/dt = -kAS \quad (3.38)$$

or

$$dC/dt = KAS/V \quad (3.39)$$

where M is mass not dissolved at time t , A is the surface area, S is the solubility, and k is the intrinsic dissolution rate constant.

The rate with which the drug decomposes is given by:

$$dC/dt = -k_1 C \quad (3.40)$$

where first-order kinetics are assumed, and where k_1 is the decomposition rate constant.

The concentration profile, therefore, is governed by the following equation:

$$dC/dt = (kAS/V) - k_1 C = k_1(\beta - C) \quad (3.41)$$

where

$$\beta = (kAS/k_1 V) \quad (3.42)$$

This may be rewritten

$$dC/(\beta - C) = -k_1 dt \quad (3.43)$$

which integrates to

$$\ln[\beta - C] = -k_1 t + \ln[\beta - C_0] \quad (3.44)$$

The value of β may be found by iteration, and this then gives both the value of S and k_1 (provided the surface area is known).

3.14. EFFECT OF SURFACTANTS

Surfactants, such as the polysorbates, will solubilize drug compounds when the surfactant is present in excess of its critical micelle concentration (CMC). Beyond this, the solubility will increase linearly with surfactant concentration.

Surfactants also aid in the wetting down of a solvent, and they are often used in dissolution tests for poorly soluble drugs.

There will be more description of this in the next chapter.

3.15. EFFECT OF PARTICLE SIZE

Ostwald (1900) and Freundlich (1922) postulated that the size of a particle affected its "solubility." The equation, known as the Ostwald–Freundlich equation, or as the Ostwald ripening effect, relates the solubilities S_1 and S_2 of particles of size r_1 and r_2 by the following equation:

$$\ln[S_1/S_2] = (4M\sigma/RT\rho)\{(1/r_2) - (1/r_1)\} \quad (3.45)$$

where σ is the interfacial energy between solid and liquid, M is molecular weight, R is the gas constant, T is absolute temperature, and ρ is density. The derivation of this will be shown in Chapter 6, on crystallization.

Taken to its fullest, the equation predicts that real equilibrium exists only between an infinitely large amount of liquid with a single, infinitely large crystal.

The equation is difficult to prove experimentally and, with prevalent values of the factor $(4M\sigma/RT\rho)$, real differences would be difficult to detect when r is larger than $0.1 \mu\text{m}$. Attempts at this have been made (Smolen and Kildsig, 1971; Krause and Kildsig, 1972; Jeannin et al., 1975), but the equation has also been refuted (Bikerman, 1970).

One reality of the equation is that, in polydisperse suspensions, smaller particles often disappear at the expense of larger ones (ripening), but other circumstances (temperature fluctuations) could also account for this.

SYMBOLS

A = constant in the extended Van't Hoff solubility equation

$[A]$ = concentration of A , ligand or substrate

A_1 = thermodynamic function of component A

A_2 = Thermodynamic function of component B

A_i = thermodynamic function of mixture

$\partial A_1/\partial n_1$ = partial molal thermodynamic function of component A

$\partial A_2/\partial n_2$ = partial thermodynamic function of component B

$\partial A_i/\partial x$ = slope of thermodynamic function versus composition (x) curve

a_s = activity of component A in saturated solution

B = constant in the extended Van't Hoff solubility equation

$[B]$ = concentration of B, substrate or ligand

C = concentration

Δc = heat capacity difference between component A in solution and solid component A.

f_a, f_b = volume fractions two solvents A and B when no solute is present

$\partial H_i / \partial n_1$ = slope of integral heat versus composition (n) curve

$\partial H_1 / \partial n_1$ = partial molal enthalpy of component A

$\partial H_2 / \partial n_2$ = partial molal enthalpy of component B

$\Delta H = -(h_s - h^0)$ = enthalpy of solution, enthalpy associated with transferring 1 mol of solid into a (large quantity of) saturated solution

ΔH_v = heat of vaporization

h^0 = enthalpy of solid

h_s = enthalpy of component A in saturated solution R = gas constant

K = complexation constant

M = (a) molecular weight or (b) counter ion

$[M]$ = concentration of metal counter ion, M

r_1 = size of a large particle

r_2 = size of a smaller particle

S = solubility of component A

S_1 = solubility of large particle

S_2 = solubility of smaller particle

T = absolute temperature

V = molar volume

n_1 = number of moles of component A

n_2 = number of moles of component B

x = mole fraction

X_a, X_b = solubility in mole fraction of a compound in neat solvents A and B

β = constant in the Van't Hoff equation for solubility

$\beta_0, \beta_1, \beta_2$ = least-squares-fitted constants in Eq. (3.37)

γ_s = activity coefficient of component A in saturated solution

δ = Hildebrand solubility parameter

μ_s = chemical potential of component A in saturated solution

μ^0 = standard chemical potential of component A in solution

ρ = density

σ = interfacial tension between solid and liquid

REFERENCES

Acree WE Jr (1991). *Thermochim Acta* 178:152.

Acree WE Jr (1992). *Thermochim Acta* 198:71.

Acree WE Jr (1996). *Int J Pharm* 127:27.

Aguiar AJ, Krc J Jr, Kinkel AW, Samyn JC (1967). *J Pharm Sci* 56:847.

Ahmed SM, Naggi A, Guerrini M, Focher B (1991). *Int J Pharm* 77:247.

Barzegar-Jalali M, Hanaee J (1994). *Int J Pharm* 198:281.

Barzegar-Jalali M, Jouyban-Gharamaleki A (1996). *Int J Pharm* 140:237.

Bikerman JJ (1970). *Physical Surfaces*. Academic Press, New York, 216.

- Bogdanova S, Sidzhakova D, Karaivanova V, Georgieva S (1998). *Int J Pharm* 163:1.
- Brønsted JN (1909). *Z Phys Chem* 68:700.
- Brønsted JN (1933). *Fysisk Kemi*. Munksgaard, Copenhagen, p 139.
- Brønsted JN (1933b). *Fysisk Kemi*. Munksgaard, Copenhagen, p 140.
- Brønsted JN (1933c). *Fysisk Kemi*. Munksgaard, Copenhagen, p 141.
- Bustamante C, Ochoa R, Reillo A, Escalera JB (1994). *Chem Pharm Bull* 42:129.
- Bustamante C, Ochoa R, Reillo A, Escalera JB (1994). *Chem Pharm Bull* 42:129.
- Carstensen JT (1977). *Formulation and Preparation of Dosage Forms*. Polderman J, ed. Elsevier/North-Holland Biomedical, Amsterdam, pp 197–215.
- Chen A, Zito S, Nash R (1994). *Pharm Res* 11:398.
- Diaz D, Bernard MJB, Mora JG, Lianos CME (1998). *Pharm Dev Technol* 3:395.
- Denbigh K (1961). *The Principles of Chemical Equilibrium*. Cambridge University Press, London, p 257.
- Duchene D, Wouessidjewe D (1996). In: Dumitriu S, ed. *Pharmaceutical and Medical Applications of Cyclodextrins*. Marcel Dekker, New York, pp 575–602.
- Escalera JB, Bustamante P, Martin A (1994). *J Pharm Pharmacol* 46:172.
- Fawzi M, Davison E, Tute M (1980). *J Pharm Sci* 69:104.
- Freundlich H (1922). *Colloid and Capillary Chemistry*. Dutton, New York, p 155.
- Grant DJW, Medhizadeh M, Chow AHL, Fairbrother JE (1984). *Int J Pharm* 18:27.
- Hammad MA, Müller BW (1998). *Int J Pharm* 169:55.
- Higuchi T, Connors KA (1965). *Adv Anal Chem Instr* 4:116.
- Higuchi T (1958). *J Am Pharm Assoc Sci Ed* 47:657.
- Hill AE (1931). In: Taylor HS, ed. *A Treatise on Physical Chemistry*. Van Nostrand, New York, pp 336–338; 536–539.
- Hoy K (1970). *J Paint Technol* 42:76.
- Irie T, Uekama K (1997). *J Pharm Sci* 86:147.
- Jeannin C, Pothisiri P, Carstensen JT (1975). *Ann Pharm Fr* 33:433.
- Jouyban-Gharamaleki A, Hanaee J (1997). *Int J Pharm* 154:245.
- Jouyban-Gharamaleki A, Acree WE (1998). *Int J Pharm* 167:177.
- Jozwiakowski MJ, Nguyen NT, Sisco JJ, Spankcak CW (1996). *J Pharm Sci* 87:193.
- Krause PD, Kildsig DO (1972). *J Pharm Sci* 61:281.
- Longuemard P, Jbilou M, Guyot-Hermann A-M, Guyot J-C (1998). *Int J Pharm* 170:51.
- López JR, Galán AC, Galán YCR (1987). *Cienc Ind Farm* 6:325.
- Loftsson T, Fridriksdottir H (1998). *Int J Pharm* 163:115.
- Loftsson T, Brewster ME (1996). *J Pharm Sci* 85:1017.
- Lordi N, Sciarrone B, Ambrosio T, Parta AN (1964). *J Pharm Sci* 53:463.
- Malaviolle I, DeMaury G, Chauvet A, Terol A, Masse J (1987). *Thermochim Acta* 121:283.
- Marshall AL (1931). In: Taylor, HS, ed. *A Treatise on Physical Chemistry*. Van Nostrand, New York, pp 336–338; 336–339.
- Martin A, Newburger J, Adjei A (1980). *J Pharm Sci* 69:487.
- Martin A, Paruta AN, Adjei A (1981). *J Pharm Sci* 70:1115.
- Martin A, Wu PL, Liron Z, Cohen S (1985). *J Pharm Sci* 74:638.
- Milosovich G (1964). *J Pharm Sci* 53:484.
- Ochsner AB, Belloto RJ Jr, Sokoloski TD (1985). *J Pharm Sci* 74:132.
- Ostwald W (1900). *Z Phys Chem* 34:503.
- Pudipeddi M (1966). PhD dissertation, School of Pharmacy, University of Wisconsin, Madison, WI, p 86.
- Raghavan KS, Nemeth GA, Gray DB, Hussain MA (1996). *Pharm Dev Technol* 1:231.
- Rajewski RA, Stella VJ (1996). *J Pharm Sci* 85:1142.
- Romero S, Reillo A, Escalera B, Bustamante P (1996). *Chem Pharm Bull* 44:1061.
- Smolen V, Kildsig DO (1971). *J Pharm Sci* 60:130.
- Squillante E, Needham T, Zia H (1997). *Int J Pharm* 159:171.

Sunwoo C, Eisen H (1971). *J Pharm Sci* 60:238.

Truelove J, Bawarshi-Nassar R, Chen N, Hussain A (1984). *Int J Pharm* 19:17.

Usui F, Maeda K, Kusai A, Ikeda M, Nishimura K, Yamamoto K (1997). *Int J Pharm* 170:247.

Williams NA, Amidon GL (1984). *J Pharm Sci* 79:9.

Yalkowsky SH, Roseman TJ (1981). In: Yalkowsky SH, ed. *Techniques of Solubilization of Drugs*. Dekker, New York, pp 91–134.

This Page Intentionally Left Blank

4

Particle Sizes and Diameters

4.1. Multiparticulates	52
4.2. Particle Dimensions	52
4.3. Measurements of Particle Sizes	53
4.4. Microscopy	53
4.5. Scanning Electron Microscopy	54
4.6. Permeametry (Subsieve Sizer) and Gas Adsorption Methods	54
4.7. Sieve Analysis	55
4.8. Electronic Counters and Laser Counters	56
4.9. Hydrodynamic Diameters	57
4.10. Fourier–Transformed Powder Diffuse Reflectance Infrared (FTIR) Spectroscopy	58
4.11. Particle Diameters Related to Shapes	58
Symbols	59
References	59

In the previous chapters the subdivisions of the solid has been of no importance except for the Ostwald–Freundlich equation. In general, however, solids are multiparticulates (i.e., a solid sample is usually more than one particle).

Some of the methods to be described are old and tested, but today, there are many methods available for particle size and particle distribution assessment (Washington, 1992). With a multitude of methods, it becomes important to be able to define and distinguish between the many definitions of particle size that exist (Besançon, 1990). The most important will be discussed in the following.

4.1. MULTIPARTICULATES

The three most prominent subdivisions of multiparticulates are illustrated in Fig. 4.1.

A *monodisperse* powder is one for which all the particles are the same size. A *polydisperse* powder is one, the particles of which are not the same size.

An *isometric* particle is one of which the surface s may be expressed as the ratio of the surface, s to the two-thirds power of its volume v .

$$s = \Gamma(v^{2/3}) \tag{4.1}$$

where Γ is denoted the general shape factor. This will be discussed further when shapes are discussed; here, it will suffice to say that there are three, common isometric shapes; that is, a cube (with shape factor 6), a sphere, and a right cylinder (one for which its diameter equals its height).

Example 4.1

Calculate the shape factor for a sphere.

Answer 4.1

The volume of a sphere is $d^3\pi/6$ and the 2/3-power of the volume is $d^2\{\pi/6\}^{2/3}$; the surface is πd^2 , so the ratio is $\pi/\{\pi/6\}^{2/3} = 6^{2/3}\pi^{1/3} = 4.84$.

4.2. PARTICLE DIMENSIONS

The “size” of a particle would be easy to define, if the particle were either a sphere or a cube, but once the shape of the particle deviates from that, more than one definition becomes possible.

Figure 4.2 shows two situations for which the type “diameter” must be defined. In the parallelepiped, it could be either the small dimension (the height, h) AB , the long dimension (the length, l) AC , the width or breadth, b (AG), or one of the diagonals AE or BE .

Which dimension is chosen is often a question of which measuring method is used. In microscopy both b and l may be recorded, but h is usually “hidden” because the particle lies on its short side. The same is true for the amorphous particle, but in this case one often records the diagonal.

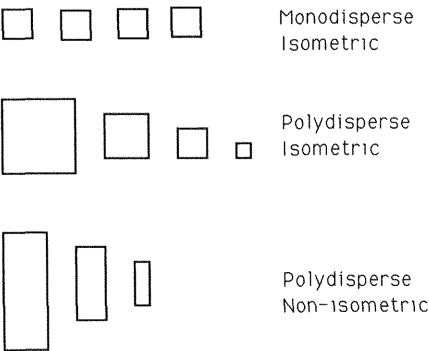


Fig. 4.1 States of subdivision.

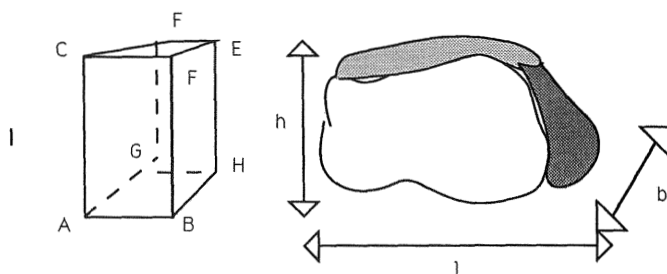


Fig. 4.2 An orthorhombic crystal (a parallelepiped) and an oddly shaped particle (e.g., an amorphous).

Isometric particles are frequently approximated by spheres. In this writing, schematic, isometric particles will always be approximated by cubes, because this shape is closer to that of a real particle.

The scientific field concerned with these matters, as well as with distributions and surface areas, is usually referred to as *micromeritics*.

4.3. MEASUREMENTS OF PARTICLE SIZES

The foregoing definitions refer to single particles, but in general, particles exist in a *population* (i.e., multiparticulate). The easiest method of differentiating between the various types of particle sizes is to describe, briefly, how they are measured. The most common methods are

- Microscopy
- Screen (sieve) analysis
- Electronic counting (Coulter, Malvern)
- Sedimentation methods (Andreasen apparatus)
- Permeametry (subsieve sizer)
- Reflectance FTIR (Otsuka and Matsuda, 1996)

In the following, the measured, or treated, particle dimension will be denoted by *a*.

4.4. MICROSCOPY

In optical microscopy, a very dilute suspension of a sample (e.g., in mineral oil) is made, and placed on a hemocytometer slide. The number of particles of a given size range in the field (e.g., between zero and 10 μm) are counted and noted, then the number between 10 and 25, and so on. The results may present themselves (in a simplified fashion) as shown in Table 4.1.

An average particle diameter would then, logically, be given by

$$(2 \times 1) + (3 \times 5.5) + (4 \times 12.5) + (1 \times 37.5) / (2 + 3 + 4 + 1) = 106/10 = 10.6 \mu\text{m}$$

This type of diameter is called the *arithmetic mean diameter* and is denoted by

$$a_n = \sum nd / \sum n \quad (4.2)$$

Table 4.1 Example of Microscopic Particle Count

Number	2	3	4	1
Particle size (<i>a</i>) μm	1	5.5	12.5	37.5

The problem with microscopic diameters is that the sample size is very small; hence, the measured diameter is not necessarily representative of the larger lot from which it was taken. It is conventional to measure in such a fashion that the total number of particles is about 300. With scanning optical microscopy (SOM), it is possible to increase the measured number considerably, but the sample size is still small.

4.5. SCANNING ELECTRON MICROSCOPY

Much larger magnifications than achievable by optical microscopy are achieved by SEM. Ceolin et al. (1997), for instance, used SEM to distinguish between trigonal and triclinic phases of carbamazepine.

4.6. PERMEAMETRY (SUBSIEVE SIZER) AND GAS ADSORPTION METHODS

In permeametry it is actually the surface area that is measured and this method will be treated in more detail at a later point. The type diameter obtained by permeametry is called the *surface volume mean diameter*. If one considers the volume *V* and the surface area *A* of a sphere, with diameter *a*, then the ratio of *V* to *A* has the dimension of a diameter

$$V/A = \{(\pi/6)a^3\}/(\pi a^2) = a/6$$

(4.3)

so that for a nonspherical particle one may generalize that

$$a_{sv} = 6v/s$$

(4.4)

a_{sv} is denoted the surface volume mean diameter. For isometric shapes this is independent of size.

Given a particle population of *n*₁ particles of diameter *a*₁, *n*₂ particles of diameter *a*₂, and so on (Table 4.2), it is seen that

$$V = \pi/6\{n_1a_1^3 + n_2a_2^3 + \cdots\} = (\pi/6) \sum na^3$$

(4.5)

$$S = \pi\{n_1a_1^2 + n_2a_2^2 + \cdots\} = \pi \sum na^2$$

(4.6)

Table 4.2 Example of Microscopic Particle Count

Number	2	3	4	1
Particle size (<i>d</i>) μm	1	5.5	12.5	37.5
<i>na</i> ³	2	499.125	7812.75	52734.38
<i>na</i> ³	2	90.75	625	1406.25

so that

$$a_{sv} = 6V/S = \sum na^3 / \sum na^2 \quad (4.7)$$

where V and S are the volume and surface area of the population (i.e., the sample).

From the sums it can be calculated that

$$a_{sv} = 28.74211 = 28.7 \mu\text{m} \quad (4.8)$$

It is easier to write a program for such conversions if they are often needed. A program in BASIC is shown in Table 4.3.

The surface-volume mean diameter is frequently called the *third-moment diameter*, and the arithmetic mean diameter is, in similar fashion called the *first-moment diameter*, the moment denoting the power of the numerator.

By obtaining the specific surface area, A_s per gram of solid, for instance, by gas adsorption (BET), surface area measurements (to be discussed later), the volume of 1 g would be

$$V = 1/\rho \quad (4.9)$$

where ρ is the density. Multiplying this by 6 and dividing by A_s would then give the surface-volume diameter

$$a_{vs} = 6/(\rho A_s) \quad (4.10)$$

Scanning electron microscopy (SEM) may be used for small particle sizes and the procedures used are quite the same.

4.7. SIEVE ANALYSIS

A very common manner of measuring particle size in industry in-process is sieve analysis (Fig. 4.3).

The openings in the screens are described by a U.S. Mesh Number, which indicates the number of strands per inch. As the wire has a width of its own, one cannot deduce the size of the opening by dividing 1 in. by the number. Table 4.4 shows common mesh sizes.

Table 4.3 Program for Converting a_n to a_{sv}

```

100 INPUT "Number of Data Sets=";Q1
110 READ N1,D1
120 Q2 = Q2 + 1
130 W1 = N1*(D1^3)
140 W2 = N1*(D1^2)
150 W3 = W3 + W1
160 W4 = W4 + W2
170 D2 = W3/W4
180 IF Q2 = Q1 GOTO 500
190 GOTO 400
400 DATA 2,1,3,5.5,4,12.5,1,37.5
410 GOTO 110
500 PRINT "Diameter=";D2

```

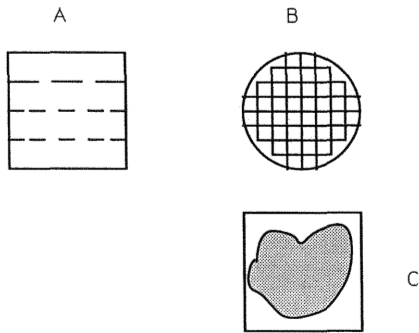


Fig. 4.3 Example of sieve analysis.

If a sieve analysis is conducted on a W gram sample, then the masses (weights) of the fractions collected on the various sieves are denoted $w_1, w_2, \dots$. Each sieve is, conventionally, assumed to collect particles of diamters of $d_1, d_2 \dots$, of which the diameters are the average values of the diameters of the confining screens. For example, a sample that went through a 60-mesh screen and was retained by a 70-mesh screen, is assumed to have an average diameter of $d = (0.25 + 0.21)/2 = 0.23$ mm or $230 \mu\text{m}$.

The “average” diameter of the entire sample may be expressed as

$$d_{\text{avg}} = d_{\text{vm}} = \sum w_i d_i / \sum w = \sum n_i d_i^4 / \sum n_i d_i^3 \tag{4.11}$$

where, $W = \sum w$. This is a fourth-moment diameter and is denoted as the weight mean diameter.

4.8. ELECTRONIC COUNTERS AND LASER COUNTERS

In the *Coulter counter*, an electrode with an aperture is employed. The electrode is placed in a dilute suspension of the drug substance, which is pumped and circulated through the aperture. The electric conductivity over the aperture is then measured. Every time a particle (with essentially negligible conductivity) passes through the aperture, the conductivity is reduced by an amount corresponding to the volume of

Table 4.4 U.S. Mesh Openings

Mesh	Opening (mm)	Mesh	Opening (mm)
10	2	80	0.177
20	0.84	100	0.149
25	0.69	120	0.125
30	0.59	200	0.074
40	0.42	230	0.063
50	0.297	270	0.053
60	0.250	325	0.044
70	0.210	400	0.037

liquid it replaces. The instrument is adjusted to a threshold value T_1 , so that only the number of particles of a given volume V_1 , is counted. This threshold is then changed to a different threshold T_2 , counting the number of particles of volume larger than V_2 , and so on, so that, in the end, results may appear as a cumulative distribution function.

The possibility of two particles passing at the same time is taken care of by a coincidence factor. It is possible to convert the cumulative distribution to a frequency function, so that one knows the number of particles n_i , that are in a certain interval of volumes, v_a and v_b . If the average of these is denoted v_i , then an average diameter can be calculated from this. This introduces the concept of a *volume mean diameter*.

$$a_v = \left\{ \sum n a_i^3 / \sum n \right\}^{1/3} \quad (4.12)$$

In a similar fashion, the Malvern counter employs a laser beam that is interfered with by particles flowing in its path. This leads to the concept of a cross-sectional definition of a diameter, denoted the *surface mean diameter*.

$$a_s = \left\{ \sum n d^2 / \sum n \right\}^{1/2} \quad (4.13)$$

Andr s et al. (1998) have shown that comparing a set of data of particle size distributions of fenofibrate, obtained by microscopy, led to a monomodal distribution, whereas laser light scattering detected a trimodal distribution, one (weak) mode about 1 μm , a size simply not detected in optical (projected) light microscopy.

4.9. HYDRODYNAMIC DIAMETERS

The Andreasen apparatus (Fig. 4.4) depends on Stokes law. Particles from a population are sampled and added to water to a concentration no larger than 2%. Usually, sodium metaphosphate is added as a deglomeration agent.

If the particles have a hydrodynamic radius of a , then the steady-state velocity v of a particle, with a density that is $\Delta\rho$ larger than the dispersion medium with viscosity η will be given by

$$v = 2(\Delta\rho)g/(9a^2\eta) \quad (4.14)$$

where g is gravitational acceleration. The suspension is dispersed, and at time zero, a sample is taken through the stopcock. An assay of this then gives the analytical concentration C of solids in the dispersion. At a given time t , the procedure is repeated. Particles, larger than $a_t = [9\eta 20/(2\Delta\rho t)]$ will have passed the 20-cm mark B . The new concentration C_1 may now be used to calculate the fraction, $(C - C_1)/C$ of particles with a particle size larger than a_t .

By modern standards, the method is slow, but it has several advantages:

1. The sample size is large compared with other methods.
2. It gives, directly, the oversize distribution.
3. It gives a defined radius (the hydrodynamic radius).

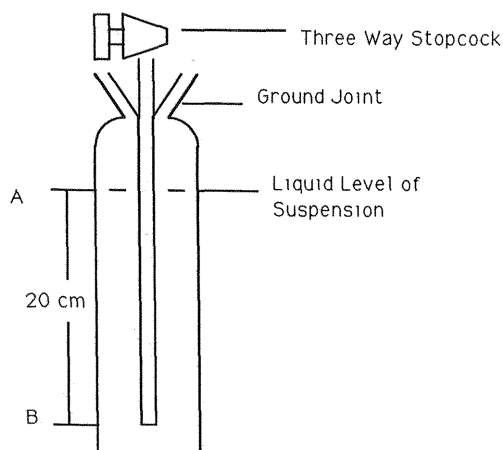


Fig. 4.4 Andreasen apparatus: At a given time t , particles possessing a radius that is larger than $a_t = [9\eta 20 / (2\Delta\rho t)]$ will be below the mark B. These particles, therefore, will not be pipetted out.

4.10. FOURIER-TRANSFORMED POWDER DIFFUSE REFLECTANCE INFRARED (FTIR) SPECTROSCOPY

Otsuka and Matsuda (1996) have described the use of FTIR reflectance spectroscopy as a method for measuring particle size distributions. For this, the sample size is larger than in the other “precision” methods.

The obtained results give good correlation between diameters observed and those observed from some (but not all) of the other methods mentioned.

It was mentioned earlier that it is important to distinguish between the various kinds of diameters, and the quoted article does not do that, leading to some speculation about why the diameter values from the FTIR diffuse method differed from a value obtained by SEM.

4.11. PARTICLE DIAMETERS RELATED TO SHAPES

We will mention more about particle diameters related to their shapes as this text progresses. Suffice it to say at this point, that there are several ways of expressing “diameters.”

Diameters are often determined microscopically. One presentation method for accounting for the shape is the *projected surface area diameter*, which is the diameter of a circle with the same area as the particle. The actual *geometric surface area* (the area calculated from the geometry of the particle, assuming it to be completely smooth) is often calculated. The *elongation factor* is the ratio of largest to smallest diameter (diagonal) is used as a measure of particle shape.

Another method is the *Heywood factor*, which attempts to describe the circularity of the particle projection (microscopically). It is the ratio of the particle diameter to the perimeter of the circle with the same area as the particle. If the shape is close to circular, then the Heywood factor will be close to unity.

Chebli and Cartilier (1998) have determined that samples of microcrystalline cellulose (MCC; Avicel PH101) and cross-linked cellulose (CLC) of particle diameters of about 50 μm and found their Heywood factors to be 125 and 179, respectively.

SYMBOLS

a = size, diameter

$a_n = \Sigma nd / \Sigma n$, arithmetic mean diameter

$a_{sv} = \Sigma nd^3 / \Sigma nd^2$, surface volume mean diameter

$a_v = \{\Sigma nd^3 / \Sigma n\}^{1/3}$, volume mean diameter

$a_s = \{\Sigma na^2 / \Sigma n\}^{1/2}$, surface mean diameter

a_t = hydrodynamic radius

A_s = specific surface area, area per gram

h = height (small dimension) of a particle AB

l = the long dimension of a particle

b = breadth of a particle

$d_{wm} = \Sigma w_i d_i / \Sigma w = \Sigma n_i d_i^4 / \Sigma n_i d_i^3$ weight mean diameter in sieve analysis

d_i = average diameter in sieve analysis, which equals average of confining screen openings

g = gravitational acceleration

i = running index

t = time

s = surface of a single particle

S = surface area of a population (sample)

v = (a) volume of a single particle; (b) Stokes velocity

V = volume of a population (sample)

$W = \Sigma w_i$ = weight of a sample for sieve analysis

Γ = overall shape factor

$\Delta\rho$ = difference in densities of solid and liquid in a settling suspension

η = viscosity

REFERENCES

- Andr s C, Bracconi P, R ginault P, Blouquin P, Rochat MH, Pourcelot Y (1968). *Int J Pharm* 167:129.
- Besa on P, Chastang J, Lafaye A, Lafaye JM (1990). *Powder Technol* 60:205.
- Ceolin R, Toscanini S, Gardette M-F, Agafonov VN, Dzyabchenko AV, Bachet B (1997). *J Pharm Sci* 86:1062.
- Chebli C, Cartilier L (1998). *Int J Pharm* 171:101.
- Otsuka M, Matsuda Y (1996). *J Pharm Sci* 85:112.

This Page Intentionally Left Blank

5

Micromeritics

5.1. Diameter Definitions	62
5.2. Distribution Types	62
5.3. Lognormal Distributions: The Hatch–Choate Relations	63
5.4. Microscopy	65
5.5. Adsorption Isotherms	66
5.6. Freundlich Isotherms	67
5.7. Langmuir Adsorption Isotherms	67
5.8. BET (Brunauer, Emmett, and Teller) Isotherms	69
5.9. Isosteric Heat of Adsorption	74
5.10. Assumptions in Adsorption Models	75
5.11. Porosity	75
5.12. Permeametry (Carman–Kozeny Equation)	78
5.13. Surface Areas from Particle Size Distributions	79
5.14. Shape Factors	79
5.15. Shape Factors by Way of Fractal Dimensions	81
5.16. Measurement Methods of Polydisperse Particle Populations	85
Symbols	85
References	87

Multiparticulates most often, as seen in the last chapter, are not monodisperse; they contain a spectrum of particle sizes. The expected distributions will be overviewed in

the following. Before discussing this it is worthwhile to have an overview of the concept and the definitions associated with “diameters” or “sizes.”

5.1. DIAMETER DEFINITIONS

There are three commonly used dimensions employed in microscopy. For crystalline materials, one uses height, length, and breadth. For amorphous materials, there are several ways, some of which also apply to crystalline samples. The diameter of a circle with the same area as the (microscopically determined) cross-section of the particle is one, the Martin’s and the Feret’s diameters are two others. These are shown in Fig. 5.1.

Martin’s diameter is along a line that dissects the particle in two equal areas. Quoting Herdan (1961) “Feret’s diameter is the mean length of the distance between two tangents on the opposite sides of the apparent outline of the particle parallel to an arbitrarily fixed direction and irrespective of the orientation of each particle coming up for inspection . . .”

There are different definitions for diameters, some of which have already been discussed. They are repeated in Table 5.1 for convenience, and include some definitions not yet touched on.

5.2. DISTRIBUTION TYPES

The most common distributions of numbers are normal, lognormal, Weibull, Poisson, and binary. The latter two are not too significant in distributions of multi-particulates, but the former, as well as bimodal distributions are.

The normal frequency function, $f(a)$ is given by

$$f(a) = \{1/\sigma(2\pi)^{1/2}\} \exp\{(a - a_{\text{avg}})^2/2\sigma^2\} \quad (5.1)$$

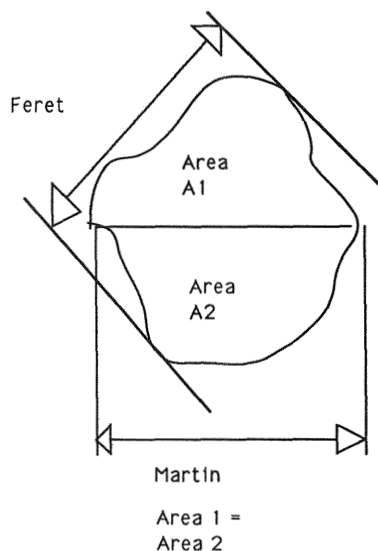


Fig. 5.1 Schematic showing the definitions of a Martin and a Feret diameter.

Table 5.1 Diameter Definitions^a

$\Sigma na / \Sigma n = a_n$:	arithmetic mean diameter
$\Sigma na^3 / \Sigma na^2 = a_{sv}$:	surface volume mean diameter
$\Sigma na^4 / \Sigma na^3 = a_{wm} = a_{vm}$:	weight mean diameter ^b
$\{\Sigma na^3 / \Sigma n\}^{1/3} = a_v$:	volume mean diameter ^b
$\{\Sigma na^2 / \Sigma n\}^{1/2} = a_s$:	surface mean diameter

^aThe symbol a denotes size or “diameter.”

^bThis notation has been used in this text to distinguish between two diameters. The “weight mean diameter” is, at times, referred to as “the volume mean diameter,” but to avoid confusion that convention will not be followed in this text.

where f denotes “function of,” a is “diameter” (or size), a_{avg} is average “diameter” (or size), and σ is the standard deviation of the population. The normal distribution function is the integral of this function. The probability of a particle having a diameter smaller than a^* is then given by

$$Pr(a < a^*) = \{1/[\sigma(2\pi)^{1/2}]\} \int_0^{a^*} \exp\{(a - a_{\text{avg}})^2/[2\sigma^2]\} da \quad (5.2)$$

The lognormal distribution is defined in Sec. 5.3. The Weibull distribution has the following form:

$$\ln\{-\ln[j]\} = -\ln[a] + C \quad (5.3)$$

where j is cumulative frequency.

The most common distribution encountered in multiparticulate solids is the lognormal distribution.

5.3. LOGNORMAL DISTRIBUTIONS: THE HATCH-CHOATE RELATIONS

Often distributions are lognormal, in that, instead of plotting sizes (diameters) on the x -axis of a frequency plot or a distribution plot, one plots the logarithms of the sizes. The mean diameter is denoted d_g (*the geometric mean diameter*).

Hence, this is defined by Eq. (5.4).

$$\ln[d_g] = \left\{ \sum n_i \ln[d_i] / \sum n_i \right\} \quad (5.4)$$

where d represents some of the aforementioned diameters. The presentation in distributional form is then given by

$$d[f(a)] = \{1/[\ln(\sigma)(2\pi)^{1/2}]\} \exp\{(\ln[d] - \ln[d_g])^2/2[\ln^2 \sigma]\} \quad (5.5)$$

$d[f(a)]$ is the number fraction of particles with diameters a , the logarithms of which are between $\ln[a]$ and $\ln[a] + \partial \ln[a]$, where the symbol ∂ is the differential notation (used to distinguish it from the diameter notation of a).

The number average of such a population is given by

$$\begin{aligned}
 a_n &= \sum na / \sum n = \sum af(a) \\
 &= \left[1 / \left[(\ln(\sigma) : (2\pi)^{1/2} \int_0^\infty a \exp \left\{ (\ln[a] - \ln[a_g]) / 2^{1/2} \{\ln \sigma\} \right\}^2 \partial \ln[a] \right] \right] \quad (5.6)
 \end{aligned}$$

The following substitution is now made:

$$u = (\ln[a] - \ln[a_g]) / 2^{1/2} \ln \sigma \quad (5.7)$$

so that when $a = 0$, $u = -\infty$. This may be rearranged to

$$\ln[a/a_g] = u[2^{1/2} \{\ln \sigma\}] \quad (5.8)$$

or

$$a = a_g \exp\{u[2^{1/2} \{\ln \sigma\}]\} \quad (5.9)$$

It is noted that

$$du = \{1/2^{1/2} [\ln \sigma]\} \partial \ln[a] \quad (5.10)$$

Inserting these equations into Eq. (5.6) now gives

$$a_n = [\sqrt{2} \ln[\sigma] / \ln[\sigma] \sqrt{2\pi}] \int_{-\infty}^{\infty} a_g \exp\{\sqrt{2} \ln[\sigma] u - u^2\} du \quad (5.11)$$

The term under the exponent sign may be rewritten

$$\sqrt{2} \ln[\sigma] u - u^2 = -\{u - (\sqrt{2}/2) \ln[\sigma]\}^2 + 0.5 \ln^2 \sigma \quad (5.12)$$

The substitution

$$m = u - (\sqrt{2}/2) \ln[\sigma] \quad (5.13)$$

is introduced, noting that

$$dm = du \quad (5.14)$$

and this inserted in Eq. (5.11) gives

$$\begin{aligned}
 a_n &= (d_g / \sqrt{\pi}) \int_{-\infty}^{\infty} \exp\{0.5 \ln^2 \sigma\} \exp(-m^2) dm \\
 &= (a_g / \sqrt{\pi}) \{0.5 \ln^2 \sigma\} 2(\sqrt{\pi}/2) = \exp(0.5 \ln^2 \sigma + \ln a_g)
 \end{aligned} \quad (5.15)$$

where use has been made of the gamma function in the evaluation of the integral. Eq. (5.15) may be rewritten

$$\ln[a_n] = 0.5 \ln^2 \sigma + \ln a_g \quad (5.16)$$

and is the first of the Hatch–Choate equations.

The remaining equations are shown in Table 5.2 [Eq. (5.16) has been repeated for convenience].

The relations correlate the *mean diameters* of number distributions with those of weight distributions; however, one of the distributions may be truly lognormal, accordingly, the other will not, but the mean diameter calculated on the assumption of lognormality would have the value stated in the table.

Table 5.2 The Hatch–Choate Relations^a

Relation	Equation no.
$\ln[a_n] = \ln[a_g] + 0.5 \ln^2 \sigma$	(5.16)
$\ln[a_s] = \ln[a_g] + \ln^2 \sigma$	(5.17)
$\ln[a_v] = \ln[a_g] + 1.5 \ln^2 \sigma$	(5.18)
$\ln[a_{sv}] = \ln[a_g] + 2.5 \ln^2 \sigma$	(5.19)
$\ln[a_g] = \ln[a_g^w] + 2.5 \ln^2 \sigma^w$	(5.20)
$\ln[a_n] = \ln[a_g^w] - 2.5 \ln^2 \sigma^w$	(5.21)
$\ln[a_s] = \ln[a_g^w] - 2 \ln^2 \sigma^w$	(5.22)
$\ln[a_v] = \ln[a_g^w] - 1.5 \ln^2 \sigma^w$	(5.23)
$\ln[a_{sv}] = \ln[a_g^w] - 0.5 \ln^2 \sigma^w$	(5.24)

^aSuperscript *w* implies distribution by weight, and lack of superscript implies distribution by number. For diameter definitions consult Table 5.1 or list of symbols at the end of the chapter.

5.4. MICROSCOPY

For *narrow* particle size, distributions are often normal. The equation for this type of distribution is Eq. (5.1).

In microscopy, a very small sample is taken from the population and a slide is prepared (usually a very dilute suspension in oil). A measuring device (e.g., a hemocytometer) allows the viewer to count the number of particles in certain particle ranges. An example of this from microscopy is shown in Table 5.3.

The *Z*-values are found from normal error curve tables.

The frequencies may be presented in histogram form, but it is more advantageous to plot the *Z*-value (obtained from the cumulative frequency) as a function of particle size to see if the distribution is normal.

In Fig. 5.2, a set of similar data (40/50 mesh) are plotted in this fashion.

The data seem to be normally distributed. The least-squares equation is

$$Z = -6.8862 + 0.031355b$$

(5.25)

Table 5.3 Data Generated for 100/200 Mesh Salicylic Acid

Range (μm)	b_{avg} (μm)	Count	Frequency, f	Cumulative f	Normal <i>Z</i> -value ^a
202	215	14	0.056	0.056	−1.590
228	241	32	0.127	0.183	−0.905
254	267	43	0.171	0.354	−0.360
280	293	44	0.175	0.529	0.075
306	319	45	0.179	0.708	0.550
332	345	40	0.159	0.867	1.115
358	371	18	0.072	0.939	1.550
384	397	9	0.036	0.976	1.980
410	423	6	0.024		

^aObtained from a normal error table.

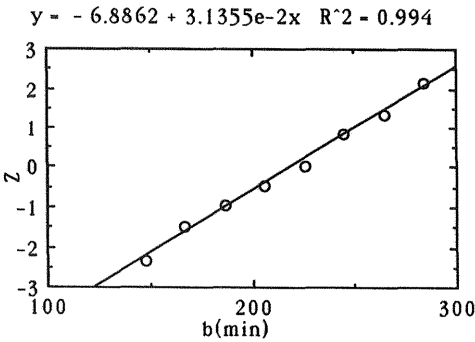


Fig. 5.2 Normalized presentation of size distributions in a 40/50 mesh cut of oxalic acid dihydrate. (Data from Dali and Carstensen, 1999.)

where b is the breadth of the particle. The mean ($Z=0$) is at

$$6.8862/0.031355 = 220 \mu\text{m} \tag{5.24}$$

and the standard deviation is

$$1/0.031355 = 32 \mu\text{m} \tag{5.25}$$

5.5. ADSORPTION ISOTHERMS

It will be seen in the following that gas adsorption is employed extensively in the measurement of surface areas. Three of the conventionally accepted types of isotherms (type I, II, and III) are shown in Fig. 5.3.

In the isotherms, the adsorbed volume of gas v is plotted as a function of pressure P of the gas. In type I isotherms v approaches an equilibrium with increasing pressure, whereas this is not true for either Type II or III, nor for the isotherm to be discussed next.

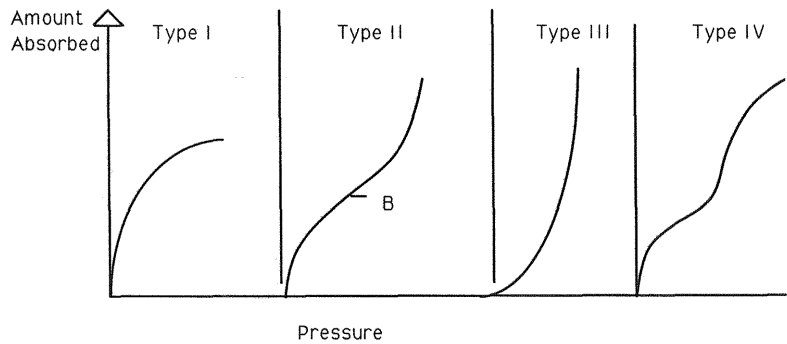


Fig. 5.3 Four of the five conventional types of gas adsorption isotherms.

5.6. FREUNDLICH ISOTHERMS

If a solid, of volume V_s mL, is suspended in a liquid (of volume V mL) in which the solid is virtually insoluble, and if this liquid before the addition contains C' mg of material per milliliter, then part of this will adsorb onto the surface of the solid. After equilibration, the supernatant is separated by centrifugation (not filtration, because filter material may also be adsorbed), and is assayed and now contains C mg/mL. The adsorbed amount m is obtained as

$$m = V(C' - C) \quad (5.26)$$

And the relation between C' and m is often given by the so-called Freundlich equation.

$$m = qC^{1/n} \quad (5.27)$$

where q and n are constants. In logarithmic terms this becomes:

$$\ln[m] = (1/n) \ln[C] + \ln[q] \quad (5.28)$$

The equation is empirical, and the value of m does not approach an asymptotic value.

5.7. LANGMUIR ADSORPTION ISOTHERMS

As mentioned, surface areas (but not particle size distributions) may be obtained from gas adsorption or, occasionally, by adsorption of solutes from liquids in which the solid is insoluble. Type I isotherms are usually explained by means of Langmuir's equation (Langmuir, 1916, 1918). It is assumed that

1. The surface of the solid is smooth.
2. There is no interaction between sites.
3. All the sites are identical.

This equation will be deduced in the following for gas adsorption, but the arguments hold equally well for solute adsorption (e.g., adsorption by a solid of dyes from a solution). This is shown schematically in Fig. 5.4.

Gas molecules will adsorb onto the surface of the solid with a rate β_+ , which is proportional to the activity a of the gas, and proportionally to the fraction $(1 - \theta)$, which is not already covered with gas.

$$\beta_+ = k_+(1 - \theta)P \quad (5.29)$$

where k_+ is the adsorption rate constant and P is the pressure

Desorption of gas will occur with a rate β_- , which is proportional to the amount covered by the gas, that is,

$$\beta_- = k_- \theta \quad (5.30)$$

where k_- is the desorption rate constant. At equilibrium the two rates will equal one another, so that

$$k_- \theta = k_+(1 - \theta)P \quad (5.31)$$

When using the terminology for the equilibrium constant K

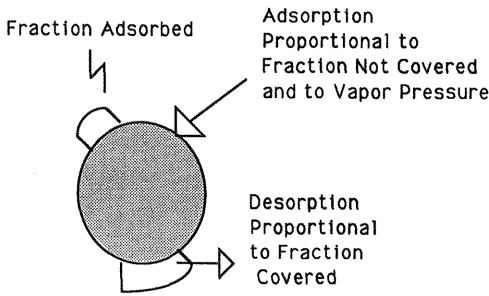


Fig. 5.4 Schematic of Langmuir adsorption.

$$K = k_-/k_+ \quad (5.32)$$

Eq. (5.32) becomes

$$\theta = KP/(1 + KP) \quad (5.33)$$

The amount of gas or solute M , which is adsorbed for each square centimeter or each gram of adsorbate would be proportional to the surface fraction covered, so that

$$M = q\theta = qKP/(1 + KP) \quad (5.34)$$

where q is a proportionality constant. Taking inverses gives

$$(1/M) = (1/q) + \{1/(qK)\}(1/P) = (1/q) + \{P_0/(qK)\}(1/a) \quad (5.35)$$

where a is the gas activity, given by

$$a = P/P_0 \quad (5.36)$$

In Figure 5.5 the asymptote is estimated at 0.151 and the surface area of the solid can be estimated from this, if the cross-sectional area of the gas or solute is known. Refinements of the asymptote calculation can be made statistically (Carstensen, 1996b). The data in Fig. 5.5 are plotted according to Eq. (5.28) to give Fig. 5.6.

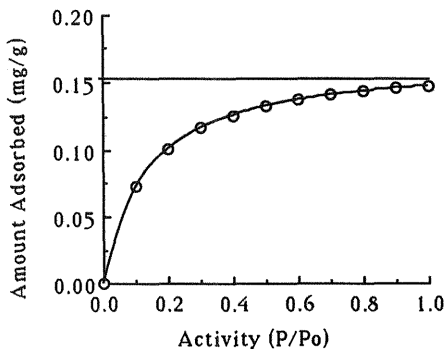


Fig. 5.5 Curve characteristic of a Langmuir isotherm.

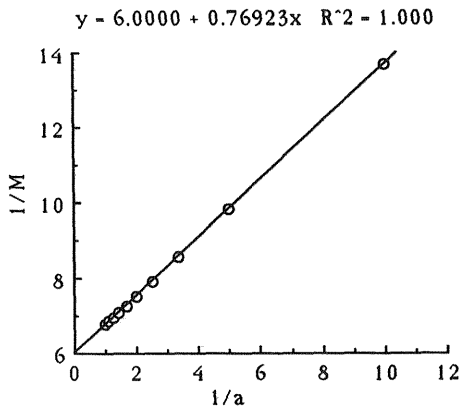


Fig. 5.6 Data from Fig. 5.4 plotted according to Eq. (5.35).

The Langmuir adsorption equation is based on the assumption that all surfaces are smooth, and that all the particle sites are equally energetic. It also assumes no nearest-neighbor interactions between sorbed molecules.

Inverse plots, in general, *cannot be obtained by plotting the inverses by least-squares fit*, and use of nonlinear programs are advocated (Carstensen, 1998).

5.8. BET (BRUNAUER, EMMETT, AND TELLER) ISOTHERMS

Type II isotherms are usually explained by the derivation of Brunauer, Emmett, and Teller (1938, 1940). The assumption made in the derivation of the Langmuir isotherm is that only one (mono-) layer is allowed. Aside from the other assumptions in the Langmuir model, the BET model assumes that multiple layers may form (Fig. 5.7).

It is assumed that the first layer may not be complete before the second forms, and the third layer may form before both of the underlayers are completed. The situation depicted is at a given pressure p . The surface area of the solid is A (m^2), and one part (s_0) is not covered. One part (s_1) has one layer, one part (s_2) has two layers, and so on. It is assumed in the following that n layers may form. The molecules adsorbed take up a volume of v_0/m^2 of layer. The volume adsorbed in Fig. 5.7 is, therefore,

$$s_0 + s_1 v_0 + 2s_2 v_0 + 3s_3 v_0 + \dots \tag{5.37}$$

The rate with which adsorption occurs on the uncovered surface (to create the first layer of adsorption) is proportional to the uncovered area s_0 . It is also proportional to the gas pressure p , and the rate constant is denoted a_1 . The subscript “1” here denotes the first layer that is sorbed. The rate, hence, is $a_1 s_0$. The desorption rate is proportional to s_1 , the area of the first-sorbed layer, and the rate constant is $k_1 = b_1 \exp(E/RT)$. Here, E is the energy required for the adsorption of the first-sorbed layer. The following equation, therefore, holds at equilibrium for the first layer.

$$a_1 s_0 p = b_1 s_1 \exp(-E/RT) \tag{5.38}$$

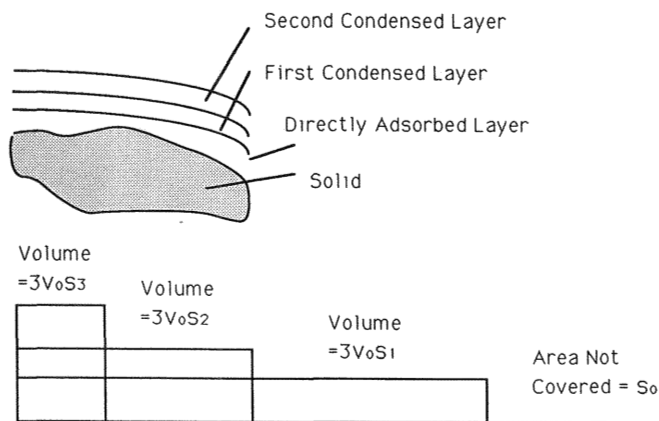


Fig. 5.7 Schematic for the assumptional mechanism in BET isotherms.

The second layer is formed by molecules sorbing on an area of $s_1(\text{m}^2)$ of the first layer, so that the sorption rate is a_2s_1p , and the desorption rate is now proportional to the surface area of the second layer (s_2), and the rate constant is $b_2\exp(-E_L/RT)$. The equation for this situation is, in analogy with Eq. (5.39),

$$a_2s_1p = b_2s_2\exp(-E_L/RT) \quad (5.39)$$

The BET treatment now makes the following assumption:

4. The value of E_L is the enthalpy of liquefaction (condensation) of the gas on the surface.
5. This value applies to all subsequent layers.

An equation similar to Eq. (5.39) may now be written for the third layer.

$$a_3s_2p = b_3s_3\exp(-E_L/RT) \quad (5.40)$$

and so on. The next approximation made is:

6. The ratio a_i/b_i is constant and simply denoted a/b for the first and higher layers (i.e., $i \neq 1$). The term

$$y = p(a_1/b_1)\exp(E_L/RT) \quad (5.41)$$

is now introduced into Eq. (5.40), which becomes

$$s_1 = ys_0 \quad (5.42)$$

and

$$x = p(a/b)\exp(E_L/RT) \quad (5.43)$$

The expression for the Clausius–Clapeyron equation in this notation, is $p_0 = (a/b)\exp(-E_L/RT)$ so that

$$x = p/p_0 \quad (5.44)$$

where p_0 is the equilibrium pressure for a bulk mass of the adsorbent at the temperature T of the experiment.

$$s_2 = xs_1 \quad (5.45)$$

In general

$$s_i = s_{i-1}x \quad (5.46)$$

so that

$$s_i = s_1x^{i-1} \quad (5.47)$$

One now denotes

$$c = y/x \quad (5.48)$$

so that

$$c = \{[a_1/b_1]/(a/b)\} \exp\{(E - E_L)/RT\} \quad (5.49)$$

We may hence combine Eqs. (5.47) and (5.48) to read

$$s_1 = cs_0x \quad (5.50)$$

The total area (see Fig. 5.7) is given by

$$A = s_0 + s_1 + s_2 + \cdots s_n = s_0 + s_0cx + s_0cx^2 + \cdots s_0cx^n = s_0\{1 + c\Sigma ix^i\} \quad (5.51)$$

As seen in Fig. 5.7 the total volume v , of adsorbant is

$$\begin{aligned} v &= v_0\{s_1 + 2s_2 + 3s_3 + \cdots ns_n\} = v_0\{cs_0x + 2cs_0x^2 + 3cs_0x^3 + \cdots ncs_0x^n\} \\ &= cs_0v_0\Sigma ix_i \end{aligned} \quad (5.52)$$

The aim is to find the value of the volume v_m , of an adsorbed monolayer, because it may be converted to the number of molecules that are adsorbed and, knowing their effective cross section, the area of the solid A may be calculated. From the beginning and Eq. (5.50) it follows that

$$v_m = Av_0 = v_0s_0\{1 + c\Sigma x^i\} \quad (5.53)$$

By combining Eqs. (5.51) and (5.53), Eq. (5.54) is obtained.

$$v/v_m = \{c\Sigma ix^i\}/\{1 + c\Sigma x^i\} \quad (5.54)$$

The geometric series $\Sigma x^i = x/(1 - x)$. It is also apparent that $\Sigma ix^i = x\{\partial \Sigma x^i / \partial x\} = x\{\partial [x/(1 - x)] / \partial x\} = x/(1 - x)^2$ so that introducing these terms into the summations in Eq. (5.54) will give

$$v/v_m = cx/[(1 - x)(1 - x + cx)] \quad (5.55)$$

Introducing Eq. (5.44) into Eq. (5.55) now gives

$$p/\{v(p_0 - p)\} = (1/v_m c) + [(c - 1)/v_m c](p/p_0) \quad (5.56)$$

or

$$(p/p_0)/\{v[1 - (p/p_0)]\} = (1/v_m c) + [(c - 1)/v_m c](p/p_0) \quad (5.57)$$

so that plotting the parameter $(p/p_0)/\{v(1 - (p/p_0))\}$ versus (p/p_0) should yield a straight line. If a nitrogen isotherm is carried out at liquid nitrogen temperature, then $p_0 = 1$ atm, so that it is simply a matter of plotting p , rather than p/p_0 .

Equations (5.56) and (5.57) are the BET equations, and they account for type II adsorption isotherms when c is not too large, and for large values of c , account for type III isotherms.

If plotting is carried out according to Eq. (5.57), then the slope/intercept ratio will be

$$\text{Slope/intercept} = [c - 1]/c \quad (5.58)$$

v is the amount of gas adsorbed converted to standard temperature and pressure. From the isotherm it is possible to calculate the value of v_m (and c) and from v_m it is possible to calculate the number of molecules N in a monolayer. For surface area measurements, nitrogen is the most frequently used gas (krypton is also employed). Nitrogen has a projected adsorbed area of $16 \text{ \AA}^2 = 16 \times 10^{-16} \text{ cm}^2$, so that the area of the solid measured would be $16 \times 10^{-16} N$. Brunauer et al. (1959, 1961) later noted that nitrogen adsorption often gives low results, and quotes that for tobermorite the surface areas ranged from 20 to 90% of those obtained by water adsorption, and that this latter was confirmed by means of low-angle X-ray scattering. However, moisture isotherms are often associated with water bonding to "internal" sites (e.g., in the case of microcrystalline cellulose) (Marshall et al., 1974, 1975; Hollenbeck et al., 1978); thus, for *dry* solids the value obtained with nitrogen is a reliable measure of the actual surface area.

The value of surface area measurements in pharmaceuticals is its relation directly to bioavailability (because often this increases with surface area of the drug), and indirectly to dissolution rates. Because this latter is associated with *wetted* surfaces, the dry surface area may not be all that meaningful at times.

Example 5.1

Given the data in Table 5.4 for a 10-g sample of a solid, calculate the surface area and the specific surface area. The gas used is nitrogen at liquid nitrogen temperature.

Answer 5.1

When the second column is plotted versus the first a typical type II isotherm results (Fig. 5.8).

Table 5.4 Nitrogen Adsorption onto a Solid Sample

p (atm)	v (mL, STP)	$p/[v(1 - p)]$
0	0	0
0.2	23.81	0.011
0.4	32.52	0.021
0.6	49.18	0.031
0.8	98.77	0.041

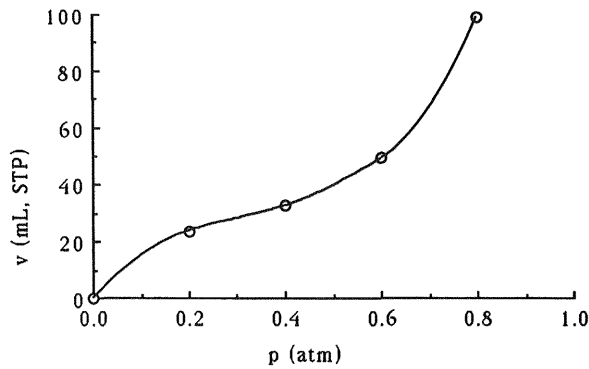


Fig. 5.8 Data from Table 5.4.

The data in Table 5.4 are now treated by way of Eq. (5.57) and shown in Fig. 5.9. It is seen that the intercept is 5×10^{-4} and the slope is 0.05, so that according to Eq. (5.58)

$$(c - 1)/c = 5 \times 10^{-4}/0.05 = 0.01 \tag{5.59}$$

that is,

$$c = 1/0.99 = 1.01 \tag{5.60}$$

The slope is

$$(c - 1)/(v_m c) = 0.01/(1.01 v_m) = 0.05 \tag{5.61}$$

so that

$$v_m = 20 \text{ mL (STP)} \tag{5.62}$$

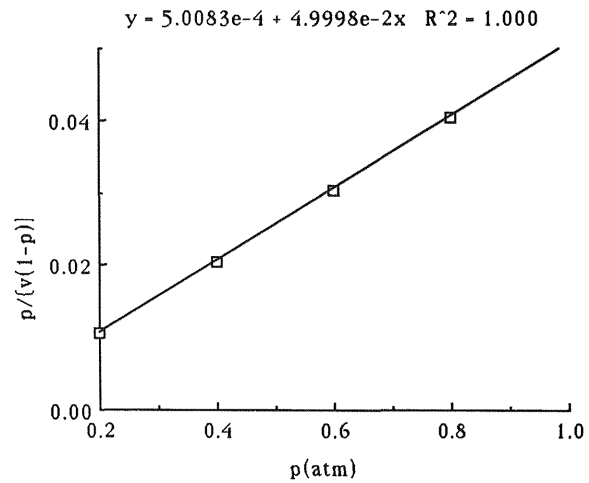


Fig. 5.9 Data in Table 5.4 treated by Eq. (5.47).

This corresponds to $20 \times 10^{-3}/22.4 = 0.893 \times 10^{-3} \text{ mol} = 5.36 \times 10^{20}$ molecules at $16 \times 10^{-8} \text{ cm}^2$; hence, the surface area of the solid sample is

$$A = [5.36 \times 10^{20}][16 \times 10^{-16}] \text{ cm}^2 = 85 \times 10^4 \text{ cm}^2 = 85 \text{ m}^2 \quad (5.63)$$

Gas adsorption measures both external (real surface) area and internal (pore volume) surface areas.

If the surface area A of a sample is divided by its mass W , then the *specific surface area*, A_{sp} , results. At times the *volumetric specific surface area*, A_s , results by dividing the surface area of a sample by its real volume.

5.9. ISOSTERIC HEAT OF ADSORPTION

Adsorption is associated with an enthalpy of adsorption, as stated in the foregoing. The isosteric heat of adsorption is obtained in the manner shown in Fig. 5.10.

The isosteric differential heat of adsorption q (Jacobs and Tompkins, 1955) is given by

$$q = RT^2\{(\partial \ln p)/\partial T\}_\theta \quad (5.64)$$

where θ is the fraction covered. The equation, strictly speaking, was derived for a Langmuir isotherm only, but may also be applied to the low-pressure region of a BET curve. If Eq. (5.64) is integrated it becomes

$$[\ln p] = -q/RT + \beta \quad (5.65)$$

where β is a constant.

Pudipeddi et al. (1995) have modified a thermal activity monitor to allow measurements of heat of adsorption directly. In so doing, they can also construct the entire adsorption isotherm.

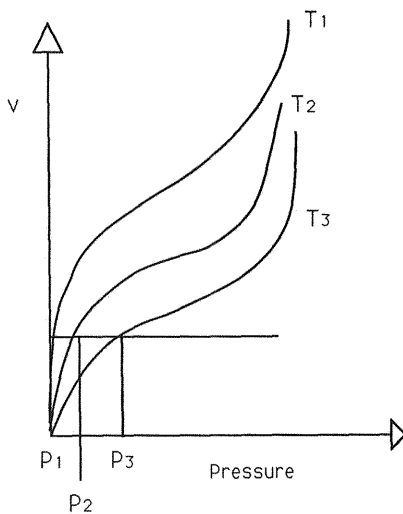


Fig. 5.10 Isotherms at three different temperatures, $T_1 < T_2 < T_3$.

5.10. ASSUMPTIONS IN ADSORPTION MODELS

There are several, rather severe assumptions in the two models presented so far. One is that of active sites. It has tacitly been assumed that all sites are equally energetic. One manner in which this may be investigated is through the isosteric heat of adsorption. If this is plotted versus temperature (i.e., if the data in Fig. 5.8 are treated at different levels of coverage), it becomes apparent at times, that there is a very distinct difference between the heat at low coverage and that at higher coverage).

In some isotherms this is directly demonstrable. Adsorption isotherms of argon on cadmium bromide at 77.5 K have been reported by Olivier (1960) and are typically of type IV (see Fig. 5.3). Ross et al. (1961) explain that "the experimental isotherm shown in [Fig. 1] can be described quantitatively by a dual distribution of the adsorptive energies."

The difference in heat of adsorption at different degrees of coverage, might also be attributable to another assumption; namely, the notion that the adsorbed layer is associated with one energy of adsorption, and all the others are unaffected by the solid, only by the heat of condensation. Guggenheim (1966), Anderson (1946), and deBoer (1968), have proposed and formulated a model, the GAB model, that accounts for an intermediate state between the first, and tightly bound layer and the bulk layer, which is associated with higher pressures.

This model will be discussed in further detail in Chapter 8, dealing with moisture isotherms.

Pudipeddi (1996), has demonstrated this directly and states:

It should be noted that in real systems the heat of interaction of the adsorbate with the solid surface is not constant as assumed by the BET or its analogous model. The heat of adsorption decreases as a function of coverage to a constant value (close to the heat of condensation of the adsorbate).

A fair amount of adsorption work is performed by the heat of immersion, first suggested by Harkins and Boyd (1942) and Jura and Harkins (1943).

5.11. POROSITY

If a solid is "all solid," then the considerations alluded to in the foregoing hold true, but most particulate solids exhibit some degree of *particle porosity*. (This is to be distinguished from *bed porosity*, which will be covered in later chapters.) A liquid condensed in a pore of radius r will have a lower vapor pressure P^* than that of the bulk liquid, P_0 , and the relation is given by the Kelvin equation:

$$\ln[P^*/P_0] = \exp[(-2\gamma V \cos \theta / RTr)] \quad (5.66)$$

where V is the molar volume of the liquid, γ is the interfacial tension between liquid and solid and θ is the contact angle. It is noted that an external vapor pressure has to exceed P^* before condensation of the "adsorbent" can begin, and this pressure is often referred to as the *breakthrough pressure*.

If all the pores have the same size and are evacuated fully, and the solid then exposed to vapor of a gas, below its critical temperature, then, as the pressure is increased in the low-pressure range, a conventional isotherm (type I or II, for instance) will result as shown by OP^* in Fig. 5.11a. Capillary condensation will

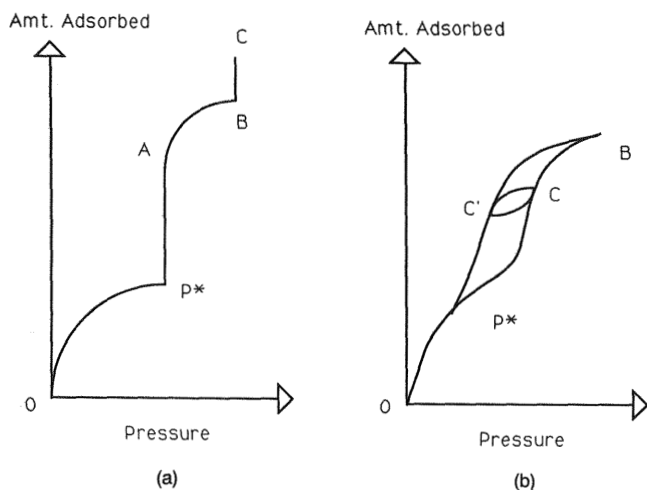


Fig. 5.11 Isotherm for vapor adsorption by an ideal (A) and a real (B) porous body. (Data from Defay and Prigogine, 1966.)

commence at point *A*, and this will continue (at the same pressure—the breakthrough pressure) until the pores are filled, and after this the adsorption (*AB*) will once again be conventional surface adsorption.

When a distribution of pore sizes occur, there will be a different breakthrough pressure for each size pore, and the situation will be as shown in Fig. 5.11b.

By hysteresis looping (*C'C*) during the desorption, it is possible to obtain the pore size distribution. For actual pore size distribution, however, mercury intrusion permeametry is the method of choice.

If there are large “pockets” in a solid of volume V^* (so-called inkwell porosity), and these are connected to the surface by smaller pores of radius r , then, the distribution will fallaciously appear as V^* larger at radius r , than it really is.

It is seen, however, that gas permeametry will account for complete surfaces (i.e., the surfaces of the pores as well). It is often the *external* surface area that is of most importance, and in such cases the area as given by gas adsorption is irrelevant.

Pore size distributions are usually elucidated by way of mercury intrusion porosimetry. For this, the contact angle is about 135° (i.e., above 90°) so that an external pressure is required to intrude the mercury into the pore. The Kelvin equation [see Eq. (5.66)] still applies, so that the smaller the pore radius r , the higher the pressure needed to obtain intrusion (Fig. 5.12)

The placing of a powder sample in a cuvette, of known volume, and filling this to a given mark, allows calculation of the apparent volume of the sample, so that the apparent density ρ' can be calculated. By now increasing the pressure of the mercury systematically and measuring the volume “outside” in the cuvette, the difference between two readings will give the volume u intruded at a given pressure P_u (Fig. 5.13). Usually, porosimeters have a maximum of 30,000 psi, but can go as high as 50,000 psi. Hence, the very smallest of pores (e.g., less than $0.01 \mu\text{m}$) will not be accounted for. The *total porosity*, ε , may be obtained from knowledge of the true density ρ^* and the apparent density, as ε is given by

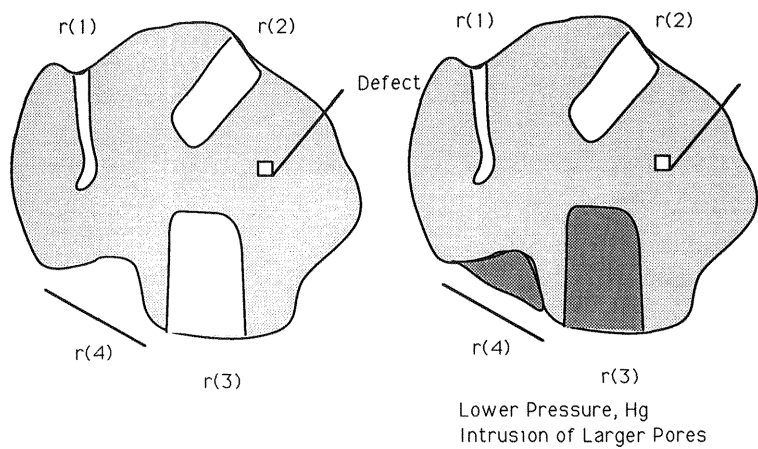


Fig. 5.12 Schematic representing pores and defects and the principle of mercury intrusion: $r(4) < r(3) > r(2) > r(1)$.

$$\varepsilon = 1 - (\rho' / \rho^*) \tag{5.67}$$

The porosity, ε_∞ , measured at the highest pressure, will be smaller than ε , and the difference $\varepsilon - \varepsilon_\infty$ can be converted to a radius that will represent the “average” of smaller pores. This unmeasured porosity represents small pores as well as defects (which are obviously not pores). The problem of inkwell pores has already been touched on.

It is apparent that the data will represent themselves as volumes u_i , representing a certain pore radius r_i , and one may, therefore, define the surface area A_p , of the particle using volume fractions w_i , as

$$A_p = \Sigma w_i \pi r_i^2 \tag{5.68}$$

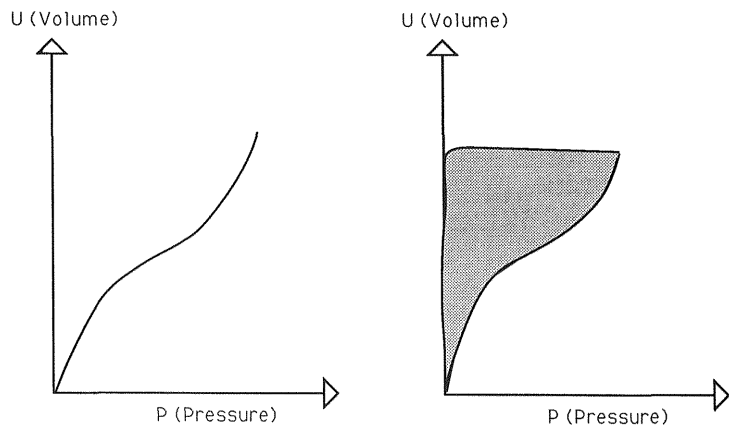


Fig. 5.13 Schematic of mercury porosimetry trace.

This is obviously based on all the pores being cylinders (the so-called bundle of cylinders model) and more directly, and more correctly, A_p may be obtained by the consideration that the work W exerted by intruding a volume of du at a pressure of P is

$$dW = Pdu \quad (5.69)$$

It is, however, also equal to the surface dA_p , times the contact angle, times the interfacial tension, so that

$$dW = \gamma[\cos \theta]dA_p \quad (5.70)$$

Equating Eqs. (5.69) and (5.70) gives

$$dA_p = Pdu/\gamma[\cos \theta] \quad (5.71)$$

Integrated this becomes

$$A_p = \{1/\gamma[\cos \theta]\} \int_{P_{\min}}^{P_{\max}} Pdu \quad (5.72)$$

where the integral represents the (cross-hatched) area under the curve in Fig. 5.13. The total volume V of the sample is known from its weight and true density; therefore, a surface-volume mean diameter, d_{sv}^* , of the pores, may formally be calculated as

$$V/6A_p = d_{sv}^* \quad (5.73)$$

5.12. PERMEAMETRY (CARMAN-KOZENY EQUATION)

External surface areas may be obtained by gas permeametry. According to Poiseuille's law for a liquid flowing under a pressure head of ΔP , a volume of V will pass through a capillary of radius r and length h in a time element t , if the viscosity of the liquid is η .

$$\Delta P/h = 8\eta V/\{\pi r^4 t\} \quad (5.74)$$

This may be rearranged to

$$\Delta P/h = 8\eta v'/\{\pi r^4\} \quad (5.75)$$

where v' is the velocity of flow through the capillary. In a powder bed with specific surface area A_s /mL of solid, and porosity ε , the so-called hydraulic radius r^* is given by

$$r^* = (1/2A_s)[\varepsilon/(1 - \varepsilon)] \quad (5.76)$$

If liquid approaches the bed with a velocity v^* , then the velocity in the pores is larger by a factor of ε , that is,

$$v^* = v'/\varepsilon \quad (5.77)$$

Introducing this expression and the expression for the hydraulic radius into the Poiseuille equation now gives

$$\Delta P/h = 32\nu'\eta(1 - \varepsilon)^2 A_s/\varepsilon^3 \quad (5.78)$$

This is the Carman-Kozeny equation (Carman, 1937, 1938; Kozeny 1927), which is employed in *permeametry* (e.g., the Fisher subsieve sizer). Here the amount of powder that corresponds to 1 cm^3 of *solid* (obtained by taking an amount of material weighing $1/\rho$ where ρ is the particle density of the solid). A tube with a cross-section of 1 cm^2 is used, so that the bed volume is the height of the bed. This allows calculation of ε . Air (or another gas of known viscosity) is now flowed through the bed at measured velocity and the pressure difference between input and efflux streams are measured. Hence, all quantities except A_s are known, and this latter can be calculated.

Because gas adsorption measures both *external and internal* (e.g., pore) volumes of a solid, and because the latter are not necessarily a part of the surface available for dissolution, permeametry is often a better means of obtaining surface areas that have meaning in dissolution testing.

5.13. SURFACE AREAS FROM PARTICLE SIZE DISTRIBUTIONS

If a particle size distribution $f(a)$ as a function of size (a) is known, then it is possible to calculate the surface area, assuming that the particles are spherical and smooth. Such a surface area is denoted the *geometric surface* area (not to be confused with the geometric mean). For a weight mean diameter-type calculation the area will be

$$A_g = \Sigma \pi w_a a^2 \quad (5.79)$$

and the weight mean diameter will be

$$d_{wm} = \Sigma w_a a / \Sigma w_a \quad (5.80)$$

Such calculations are often carried out for sieve analysis. If the external surface area A^* is known, this will be larger than A_g and the ratio, which may be attributed on an overall scale/surface *rugosity*, Ω , is given by:

$$\Omega = A^*/A_g \quad (5.81)$$

It is, as will be discussed later, possible to assign *volumetric shape factors*, α_v , to particulate solids, and this converts a "size" a (however, that is defined, e.g., Ferret diameter or projection diameter) to the particle volume v .

5.14. SHAPE FACTORS

A commonly used shape factor converts the volume of a *particle*, v , to its size, volumetric mean, a_v (see Table 5.1).

$$v = \alpha_v a_v^3 \quad (5.82)$$

Similarly a shape factor may be defined that converts the surface area s of a *particle* to its surface mean a_s .

$$s = \alpha_s a_s^2 \quad (5.83)$$

If a particle population is fairly monodisperse, such as for a narrow mesh cut, then 1 g of the cut will contain N particles, and if the particle density is ρ , then for the 1 g sample

$$Nv = N\rho\alpha_v a_v^3 = 1 \quad (5.84)$$

The surface area of the particle is $s = \alpha_s a^2$, so the specific surface area A_w is this figure divided by the mass of the particle $\alpha_v a_v^3$:

$$A_w = \alpha_s a^2 / \alpha_v a_v^3 \quad (5.85)$$

It is assumed that the narrow mesh cut is lognormally distributed, so that by introducing the appropriate Hatch–Choate relations [see Eqs. (5.17) and (5.18)] from Table 1 into Eq. (5.77) gives

$$\begin{aligned} & \ln[N\rho] + \ln[\alpha_v] + 3 \ln[a_v^3] \\ &= \ln[N\rho] + \ln[\alpha_v] + 3 \ln[a_g] + 4.5 \ln^2 \sigma = 0 \end{aligned} \quad (5.86)$$

Because N , ρ , and a_g are measurable, α_v can be calculated. A similar approach will show that

$$\ln[A_w] = -\ln[\rho\alpha_v] + \ln[\alpha_s] - \ln[d_g] - 2.5 \ln^2[\sigma] \quad (5.87)$$

where now all quantities except α_s are known so that this latter can be calculated. A prerequisite for this is that the distribution be narrow, so that Eq. (5.84) can be relied on. Another approach is tedious accounting for N by counting methods.

Shape factors may formally be calculated from microscopy, if the total number of particles per weight may be obtained experimentally. The total number of particles counted, therefore, represents a weight, which may be converted to a volume V . Because the count consists of, for each interval, listing the appropriate n_i particles of sizes length a_i and breadth b_i . The sum $\Sigma \alpha_i a_i b_i^2$ may be calculated, and assuming the height to be identical with the breadth,

$$V = \alpha_v \Sigma n_i a_i b_i^2 \quad (5.88)$$

from which α_v may be calculated. However, the assumption is made that the dimension that is hidden in microscopy, the height h is the same as the breadth. α_v may be obtained indirectly, but more logically, from dissolution data, and this will be covered in Chapter 12.

A shape factor (simply denoted *the shape factor*, Γ) is often calculated by the surface of the sample A and its true volume V by the formula:

$$\Gamma = A/(V^{2/3}) \quad (5.89)$$

For a particle the relation between α_v , α_s , and Γ is obviously given by:

$$\Gamma_i = \alpha_s / [\alpha_v^{2/3}] \quad (5.90)$$

This, however, is not correct for values of the shape factor obtained by dividing the area of a *sample* with the two-thirds power of its volume, because $[\sum n_i a_i^3]^{2/3} \neq \sum n_i a_i^2$.

5.15. SHAPE FACTORS BY WAY OF FRACTAL DIMENSIONS

The introduction of fractal geometry as a mathematical tool is attributable to Mandelbrot (1983). There are many applications of the concept, and the intent here is, first to describe what it is, and then to show how it can be applied to pharmaceutical problems.

Without delving into the intricacies of this approach, the general philosophy of it is as follows: If, for instance, the length of a contour, such as depicted in Fig. 5.14 were to be measured, then the length obtained would depend on the "length of the measuring stick," the scaling length, h ; if, for instance, this were reduced to q then the periphery measured would be longer than if one had used a larger-scaling length. This is the origin of the practical application of fractal dimensions, because interest in it started with the work of Richardson (1961), who had the task of measuring the length of the coastline of Great Britain.

In general it can be shown that the length L of a perimeter depends on the scaling length, q , by the relation:

$$\log[L] = -(1 - D)\log[q] + Q \quad (5.91)$$

where Q is a constant and D is referred to as the fractal dimension [and as demonstrated in Eq. (5.91) emerges as the negative of the slope of a logarithmic L versus q -plot]. Such plots are known as Richardson plots, coast line plots, or walking yard-stick plots, because of their origin in geographic and topological science.

An intuitive understanding of D is demonstrated in Fig. 5.15. For the straight-line on top of the figure, the dimension is 1. For the wiggly line on the bottom of the figure, the space is to a great extent filled up by the line [it is not possible to entirely fill up space with a line], and one could visualize this as having a dimension of 2. The topologic dimension is still 1, but the Euclidean dimension is 2. For the line in the middle the fractal dimension could be visualized as being between 1 and 2.

It is now possible to define the surface irregularity of a particle by the fractal dimension D [defined in Eq. (5.91)]. To do so it would be necessary, by image analysis, to obtain a cross-sectional representation of the particle and, from this,

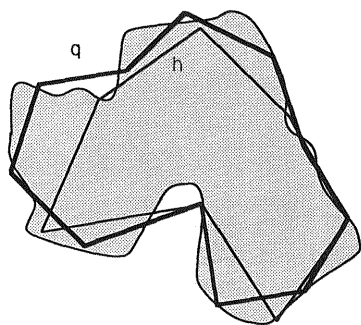


Fig. 5.14 Schematic showing principle of measurement of fractal dimensions.

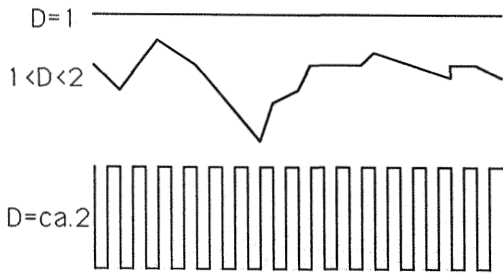


Fig. 5.15 Fractal dimensions of a contour. The curves and concepts are approximate and are shown for definition purposes only. The point where a curve becomes a plane-filling curve (e.g., a Peano curve) is complex and beyond this writing.

obtain the fractal dimension. This indeed has been done, in the pharmaceutical literature, and Fig. 5.16 is taken from the work by Ramadan and Tawashi (1990).

The slope is

$$H = 1 - D \tag{5.92}$$

the fractal *increment*, which is a measure of the surface roughness. The curve is not linear (although the authors have treated it as such). Both the photomicrographs (smooth spheres with “pimples”) published by the authors and the upper curves in their Fig. 6 imply that there are two surface populations (perimeter lengths L_a and L_b), and the same group of investigators (Thibert et al., 1988), indeed, reported later such a behavior in the fractal analysis of lactose granules; as exemplified in Fig. 5.17.

Again, there are two distinct line segments, indicating two types of surface morphology. With lactose, assumedly, fine structure of surface pores has a fractal dimension different from that of the nonporous part of the surface.

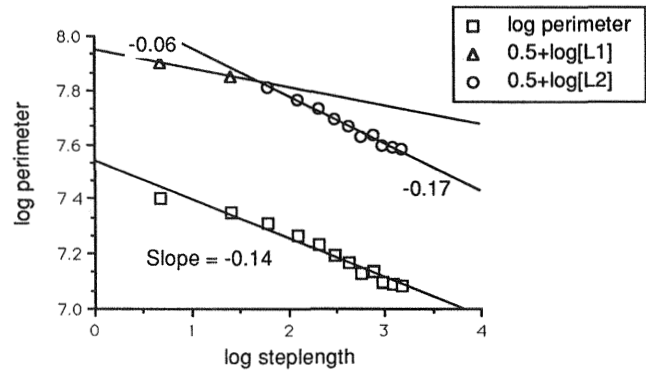


Fig. 5.16 L as a function $|$ (step length) for natural microspheres. The lower curve shows all the data plotted in simple linear regression. The points in the upper graph are those in the lower graph + 0.5. This is done for graphic clarity. In the upper graph, the points are shown as bimodal, indicating that there are two self-similarity populations. (Data from Ramadan and Tawashi, 1990.)

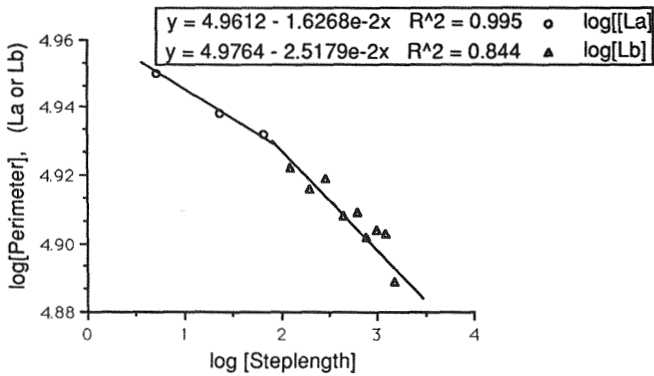


Fig. 5.17 The fractal character of lactose granulations. (Data from Thibert et al., 1988.)

Projection of cross-sectional images can be misleading in that the observation can be a function of the orientation of the solid particle. This method is better, the more spherical the particle is. It is time-consuming, and sampling (as in any other type of microscopy) represents a problem.

It is possible to probe surfaces in a more convenient manner, that is, by gas adsorption. Here the property values are averages over the entire surface; hence, sampling is less of a problem (although sample sizes are still small in such work, they are not simply one particle).

Fractal approaches to surface sampling by gas analysis are based on the principle outlined in Fig. 5.18. If a small adsorbent molecule is employed (see Fig. 5.18a), then more of the roughness will manifest itself than if a larger molecule (see Fig. 5.18b) is used. Here, again, the measured surface should be the larger the smaller the sorbed probe is.

For adsorption, the cross-sectional area of the molecule is a function its diameter h , squared. If the molecule has a circular cross-section of area b and is packed by square arrangement, then the sorbed area β is simply h^2 per molecule. Hence,

$$\beta = h^2 \tag{5.93}$$

or

$$h = (\beta)^{1/2} \tag{5.94}$$

Employing an approach similar to Eq. (5.91) gives

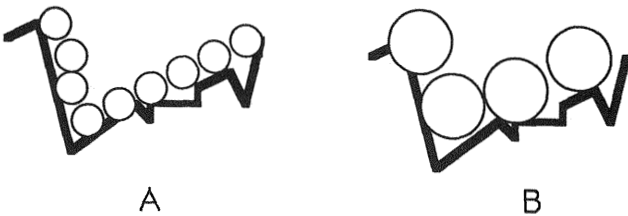


Fig. 5.18 Coverage of an irregular surface by different-sized adsorbant molecules.

$$\ln[n_m] = -D \ln[(\beta)^{1/2}] + Q = -(D/2) \ln(\beta) + Q \quad (5.95)$$

where n_m is the number of molecules in a monolayer. The more general case, where the molecular packing is other than square, packing can be treated similarly, now

$$\alpha = jh^2 \quad (5.96)$$

Figure 5.19 is constructed from data published by Avnir et al. (1983).

It is seen that the slope is

$$-D/2 = -1.0581 \quad (5.97)$$

so that

$$D = 2.16 \quad (5.98)$$

In the foregoing example, the molecules are fairly spherical, and if an adsorbent lies flat on a surface, then the fractal equation becomes

$$\log n = (-D + 1) \log[v] \quad (5.99)$$

where v is the molar volume of the sorbed molecule.

Experiments, such as those described, are still rather cumbersome, and it is more convenient (although still not practical from a quality control point of view), to do nitrogen adsorption on various mesh fractions of the solid.

Figure 5.20 shows the BET (nitrogen) surface area of different-sized fractions of Aerosil (colloidal silica). When this approach is used, the applicable equation is:

$$\log[A] = (D - 3) \log[d] + \text{constant} \quad (5.100)$$

where A is the surface area obtained by gas (nitrogen) adsorption and d is the particle diameter.

Fini et al. (1996 a,b,c) reported that the fractal dimensions often depend on the mode of crystallization. These authors (Fini et al., 1997 a,b) studied the physical properties of salts of ursodeoxycholic acid, and reported on the fractal dimensions of the surface (D_s) and the dissolution reactive dimension (D_r) as reported by Farin and Avnir (1987).

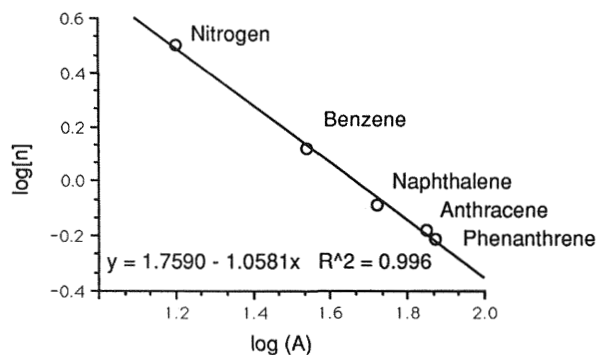


Fig. 5.19. Fractal plot of carbon black: Amount of adsorbate, n (mmol/g) in monolayer as a function of cross-sectional area ($\text{\AA}^2$) of adsorbing molecule. (Data from Avnir et al., 1983.)

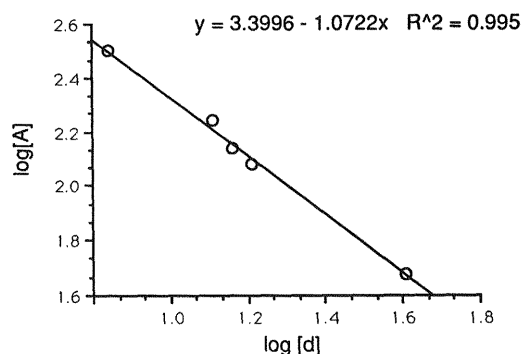


Fig. 5.20 BET surface area, A (m^2/g) as a function of particle diameter, d (nm) of various Aerosils. (Data from Avnir et al., 1983.)

5.16. MEASUREMENT METHODS OF POLYDISPERSE PARTICLE POPULATIONS

Electronic counters and laser counters are the methods of choice in many present-day situations. For instance, Zhang and Johnson (1997) used a Coulter Counter Multisizer H (Coulter Electronics, Hialeah, FL) to measure the particle size distribution of an experimental drug (CP 118 954, Pfizer). As electrolyte they use a 2% w/v solution of maleic acid, adjusted to pH of 5.4, containing 0.005% of Tween 80, after which they saturate it with drug.

Their investigation dealt with a lognormal particle size distribution, and they employed jet-milled and bantam-milled material and “spiked” it with larger particles to make the distribution log-normal by weight.

SYMBOLS

A = surface area of a sample

A^* = external surface area of porous solid (in a bed)

$A_g = \Sigma \pi w_a a^2$ = geometric surface area

A_s = surface area of a sample divided by its real volume

A_{sp} = specific surface area

A_p = surface area of the particle as

A_s = volumetric specific surface area (per cm^3 of solid)

a = (a) activity ($= P/P_0$); (b) length of a particle; (c) “diameter” (or size); (d) rate constant of adsorption (BET equation)

$a_n = \Sigma na / \Sigma n$, arithmetic mean diameter

a_{avg} = average “diameter”

b = (a) rate constant of desorption (BET equation); (b) breadth of a particle

b_i = preexponential factor for adsorption of the i th layer (BET equation)

C' = concentration before adsorption

C = concentration after adsorption

$c = y/x$ (BET constant)

D = fractal dimension

d = general size term for diameters

- d_g = geometric mean diameter = $\exp\{\Sigma n_i \ln[d_i]/\Sigma n_i\}$
 $d_s^* = V/6A_p$ = surface volume mean pore size
 d_g = geometric mean diameter = $\exp\{\Sigma n_i \ln[d_i]/\Sigma n_i\}$
 $d_{wm} = \Sigma w_a a / \Sigma w_a$ = weight mean diameter
 $d \ln[f(a)]$ = number fraction of particles with diameters a , the logarithms of which are between $\ln[a]$ and $\ln[a] + \partial \ln[a]$
 E = enthalpy of adsorption of the first layer (BET equation)
 E_L = enthalpy of condensation (BET equation)
 f = "function of"
 $f(a) = (a) \{1/[\sigma(2\pi)^{1/2}] \exp\{(a - a_{avg})^2/2\sigma^2\}$ = normal frequency function;
 (b) generally particle size distribution as a function of size (a)
 H = slope of fractal dimension plot
 h = (a) "length" of adsorbate molecule; (b) length measuring stick (in fractal dimensions); (c) length of capillary; (d) height of particle
 i = running index
 j = cumulative frequency in Weibull distribution
 K = equilibrium constant in Langmuir equation
 k_+ = rate constant of adsorption
 k_- = rate constant of desorption
 L = length of perimeter (in fractal dimensions)
 $\ln(\sigma)$ = standard deviation for lognormal distribution
 M = amount of gas adsorbed on a solid
 $m = (a) u - (\sqrt{2}/2) \ln[\sigma]$ = integral substituent dummy variable; (b) adsorbed amount (in Freundlich adsorption)
 N = number of particles in a population
 n = Freundlich exponent
 P = gas pressure
 P^* = (a) pressure that is lower than the equilibrium pressure of a gas at a given temperature; (b) breakthrough pressure in intrusion porosimetry.
 P_0 = equilibrium vapor pressure of a gas at a given temperature
 $Pr(a < a^*)$ = probability of a size a being smaller than a^*
 $Q = (a)$ Weibull distribution = $\ln\{-\ln[j]\} = -\ln[a] + C$; (b) constant (fractal dimension equation)
 $q = (a) RT^2\{(\partial \ln p)/\partial T\}_\theta$ = isosteric heat; (b) scaling factor; (c) factor in Langmuir equation; (d) Freundlich prefactor
 R = gas constant
 $r = (a)$ radius of capillary; (b) pore radius
 r^* = hydraulic radius
 r_i = pore radius of the i th pore
 s = surface area of a particle
 s_0 = surface not covered (BET equation)
 s_1 = surface covered with one adsorbent layer (BET equation)
 s_i = surface covered with i layers of adsorbent (BET equation)
 T = absolute temperature
 t = time
 $V = (a)$ molecular volume (in Kelvin equation); (b) liquid volume
 V^* = inkwell pore volume
 W = work (in mercury intrusion)

- u = (a) substituent in integral = $(\ln[a] - \ln[a_g])/2^{1/2} \ln \sigma$; (b) volume intruded at a mercury pressure of P
- v = (a) molar volume of the sorbed molecule (in fractal dimension); (b) liquid velocity; (c) volume of a particle; (d) volume of adsorbent gas at a given pressure P (BET equation)
- v' = velocity of flow
- v^* = approach velocity of a liquid to a bed
- v_0 = volume of molecules per square meter of layer
- v_m = volume of a monomolecular layer of adsorbent gas (BET equation)
- W = mass of a sample
- w_a = weight of fraction of particles with size a
- $x = p(a/b) \exp(E_L/RT)$ (BET equation)
- $y = p(a/b) \exp(-E_L/RT)$
- Z = standard normal deviate
- $\alpha = jh^2$ = scaling factor when adsorbate is not of square configuration
- $\alpha_s = a^2/s$ = surface shape factor of a particle
- α_v = volumetric shape factor of a particle = a_v^3/v
- β = square of scaling factor in three dimensions (h^2 per molecule)
- β_+ = rate with which gas molecules will adsorb onto a surface
- β_- = rate with which gas molecules will desorb from a surface
- $\Gamma = A/(V^{2/3})$ = (general) shape factor
- $\Gamma_i = \alpha_s/[\alpha_v^{2/3}]$ = (general) shape factor for a particle
- γ = interfacial tension between adsorbate and solid
- ∂ = the differential notation
- ε = particle porosity
- ε_∞ = total porosity measured at the highest intrusion pressure
- $\Omega = A^*/A_g$ = rugosity
- θ = (a) contact angle; (b) fractional coverage of a surface with adsorbed gas
- ρ' = particle apparent density
- ρ^* = true particle density
- η = viscosity
- σ = standard deviation of a population
- $\ln(\sigma)$ = standard deviation for lognormal distribution

REFERENCES

- Anderson RB (1946). J Am Chem Soc 68:686.
- Avnir D, Farin D, Pfeifer P (1983). J Phys Chem 97:3566.
- Brunauer S, Emmett PH, Teller E (1938). J Am Chem Soc 60:309.
- Brunauer S, Emmett PH, Teller E (1940). J Am Chem Soc 62:1723.
- Carman PC (1937). Trans Inst Chem Eng Lond 15:150.
- Carman PC (1938). J Soc Chem Ind 57:225.
- Carstensen JT (1996a). Modeling and Data Treatment in the Pharmaceutical Sciences. Technomic Publishing, Lancaster, PA, pp 63–73.
- Carstensen JT (1996b). Modeling and Data Treatment in the Pharmaceutical Sciences. Technomic Publishing, Lancaster, PA, p 39.
- Dali MV, Carstensen JT (1999). Drug Dev Ind Pharm 25:347.
- DallaValle JM (1943). Micromeritics. Pitman Publishing, New York, p 28.

- deBoor JH (1968). *The Dynamical Character of Adsorption*, 2nd ed. Clarendon Press, Oxford.
- Farin D, Avnir D (1987). *J Phys Chem* 91:5517.
- Fini A, Fazio G, Holgado MA, Fernández-Hervàs MJ, Rabasco AM (1996a). *Eur J Pharm Sci* 4:231.
- Fini A, Fazio G, Holgado MA, Fernández-Hervàs MJ, Rabasco AM (1996b). *J Pharm Sci* 85:971.
- Fini A, Fazio G, Holgado MA, Fernández-Hervàs MJ, Rabasco AM (1996c). *Eur J Pharm Sci* 4:231.
- Fini A, Fernández-Hervàs MJ, Holgado MA (1997a). *J Pharm Sci* 86:1303.
- Fini A, Fazio G, Fernández-Hervàs MJ, Holgado MA (1997b). *Int J Pharm* 171:45.
- Guggenheim EA (1966). *Application of Statistical Mechanics*. Clarendon Press, Oxford.
- Harkins WD, Boyd GE (1942). *J Am Chem Soc* 64:1195.
- Herdan G (1960). *Small Particle Statistics*. Butterworths, London, p 45.
- Hollenbeck RG, Peck GE, Kildsig DO (1978). *J Pharm Sci* 67:1599.
- Jura G, Harkins WD (1943). *J Chem Phys* 11:561.
- Kozeny J (1927). *Royal Acad Sci Vienna Proc Class I* 136:271.
- Langmuir I (1916). *J Am Chem Soc* 38:2221.
- Langmuir I (1918). *J Am Chem Soc* 38:2221.
- Mandelbrot B (1983). *The Fractal Geometry of Nature*. WH Freeman & Co, New York.
- Marshall K, Sixsmith D, Stanley-Wood NG (1972). *J Pharm Pharmacol* 24:138.
- Marshall K, Sixsmith D, Stanley-Wood NG (1974/1975). *Drug Dev Ind Pharm* 1:51.
- Olivier JP (1960). PhD dissertation, Rensselaer Polytechnic Institute.
- Pudipedi M (1996). PhD dissertation, University of Wisconsin, p 184.
- Pudipeddi M, Sokoloski TD, Duddu SP, Carstensen JT (1995). *J Pharm Sci* 85:381.
- Richardson LF (1961). *General Systems Yearbook* 6:139.
- Ramadan MA, Tawashi R (1990). *J Pharm Sci* 79:929.
- Ross S, Olivier JP, Hinchin JJ (1961). In: Copeland LE, Beebe RA, Graham DP, Zettlemoyer AC, Zisman WA, eds. *Solid Surfaces*. American Chemical Society, Washington, DC, p 319.
- Thibert R, Akbarieh M, Tawashi R (1988). *J Pharm Sci* 77:724.
- Zhang Y, Johnson KC (1997). *Int J Pharm* 154:179.

Problems Chapter 5

1. Plot the data in Table 5.3 and ascertain whether they are normal or lognormal. Calculate the appropriate mean and the standard deviation.

6

Crystallization

6.1. Crystallization	90
6.2. Metastable Zones and Nucleation	90
6.3. Nucleation and Critical Nucleus Size	91
6.4. The Equilibrium Dilemma	92
6.5. Homogeneous Nucleation	93
6.6. Effects of Impurities	94
6.7. Yield and Metastable Zones	94
6.8. Crystal Growth	95
6.9. Log–Log Size Distributions After Homogenous Nucleation	96
6.10. Nucleation	100
6.11. Temperature and Solubility Profiles During Thermal Recrystallization	101
6.12. Particle Size Distribution After Thermal Recrystallization	102
6.13. Heterogeneous Nucleation	104
6.14. Crystal Habit	104
References	105

The last step in drug substance manufacture is purification, and this, most often, consists of recrystallization. The conditions under which this is carried out is of great importance in pharmaceuticals, because the shape of the particle may affect machinability (e.g., needle-shaped particles may logjam when they flow through a hopper), and the morphology and the shape may affect dissolution. Therefore, a discussion of some of the fundamental factors affecting crystallization is presented.

6.1. CRYSTALLIZATION

In drug manufacture (synthesis), the drug is usually not pure when the overall process is complete. For instance, succinimide has a solubility of 1 g/20 g of ethanol at 25°C and 1 g/4 g at 60°C.

As the material is produced, it may contain, for example, 5% of an impurity that has a solubility of 2 g/20 g of ethanol at 25°C. If 10 g of crude material (containing 9.5 g of pure chemical and 0.5 g of impurity) are dissolved in 40 g of ethanol at 60°C, and then cooled to 25°C, 8.5 g of pure material will then precipitate out (1 g staying in solution) and the 0.5 g of impurity will stay in solution.

Recrystallizations may also be carried out by dissolving the substance in one solvent, and adding another in which it is insoluble; thereby, precipitating out the pure chemical and (providing the solubilities allows it) keeping the impurities in solution. In this case one speaks of *reprecipitation*.

6.2. METASTABLE ZONES AND NUCLEATION

Ostwald (1899) formulated a rule of stages: when a system first starts crystallizing, it will initially create the crystal structure that forms the smallest loss of free energy, and these crystals will later transform, stagewise, to the most (or a more) stable crystal structure. This will be dealt with further in Chapter 8.

It is a common misunderstanding that precipitation and recrystallization occurs from saturated solutions, whereas they actually occur from *supersaturated* solutions.

This is illustrated in Fig. 6.1. If 300 mg of material is added to 1 g of solvent and heated to 70°C (point B), then it will go into solution. On cooling, however, it will not precipitate until point A (57°C). The width of this zone (AB) is denoted the metastable zone.

Nyvt (1971) has shown that the width of the zone may be a function of to how high a temperature the solution has been heated and for how long. That is, if, in the foregoing example, the heating was carried out at 90°C, then the zone would be

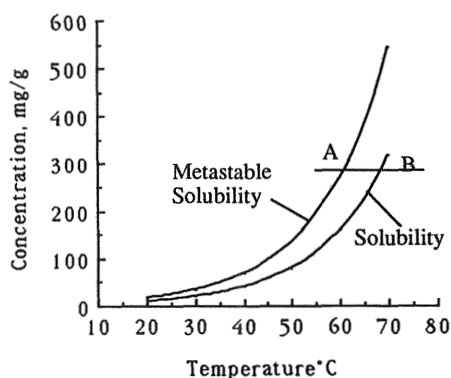


Fig. 6.1 If, for instance, a solution at 300 mg/g is heated to 70°C (point past B), and then cooled, precipitation will not occur (in a reasonable length of time) until 57°C (A) is reached.

wider, and if it were kept there for 1 h, rather than for 5 min, it would then also be wider.

It is speculated that complete randomness of the solution is not ascertained until it has been kept at a temperature well above the solution temperature and for a given length of time, and that if complete randomness is not at hand, then the nucleation will occur more readily.

6.3. NUCLEATION AND CRITICAL NUCLEUS SIZE

In this chapter, the symbol r denotes dimension (radius, diagonal). For a cubical nucleus of size r

$$\Delta G = -\mu r^3 + 6\sigma r^2 \quad (6.1)$$

where μ is chemical potential and σ interfacial tension. ΔG is maximum when

$$d\Delta G/dr = -\mu 3r_m^2 + 12\sigma r_m = 0 \quad (6.2)$$

that is, when

$$r_m = 4\sigma/\mu \quad (6.3)$$

This then is the critical nucleus size, because beyond this size, the growth of a nucleus is accompanied by a negative ΔG (Fig. 6.2).

The argument that follows is, strictly speaking, incorrect (Bikerman, 1970). It is given in its classic form in Carstensen (1980).

If we talk about solubility, then ΔG from solid to solution must be zero. μ is the chemical potential per cubic centimeter (cm^3), so to determine it per mole, it must be divided by the density ρ (to obtain the chemical potential per gram) and be multiplied by the molecular weight (MW) to obtain the chemical potential per mole.

$$(\text{MW}/\rho)\{-\mu r_s^3 + 6\sigma r_s^2\} = 0 \quad (6.4)$$

where r_s is the dimension at solubility. Therefore,

$$(\text{MW}/\rho)\{\mu r_s^3\} = (\text{MW}/\rho)\{6\sigma r_s^2\} \quad (6.5)$$

or

$$(\text{MW}/\rho)\{\mu\} = (\text{MW}/\rho)\{6\sigma/r_s\} \quad (6.6)$$

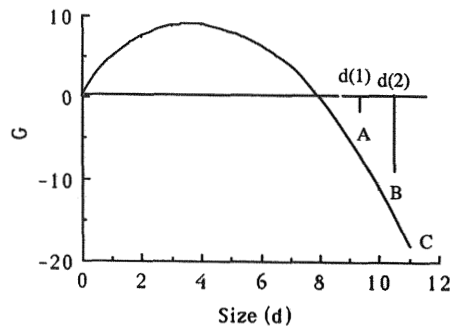


Fig. 6.2 Chemical potential and nucleus size.

But the left-hand side of the equation is $\Delta G_o + RT \ln[C_s]$, where ΔG_o refers to standard state, so

$$\ln[C_s] = [(MW6\sigma/\rho)][1/r_s][1/(RT)] - [\Delta G_o/(RT)] \quad (6.7)$$

If a system is taken from point A (with dimension r_1) to point B (with dimension r_2), then

$$\Delta G = [6(MW\sigma/\rho)][(1/r_2) - (1/r_1)] \quad (6.8)$$

But this means that

$$\ln[C_{s2}/C_{s1}] = 6(MW\sigma/\rho)[(1/r_2) - (1/r_1)] \quad (6.9)$$

This is known as the Ostwald–Freundlich equation (Ostwald, 1898).

The equation, seemingly, predicts that solubility is inversely proportional to the size of a particle, but there are problems with the argument, in that ΔG cannot be zero all along the curve.

6.4. THE EQUILIBRIUM DILEMMA

Equation (6.7) predicts that the equilibrium state of a solid is an infinitely large crystal, or more correctly, it predicts that if a multiparticulate system is placed in a liquid, then the crystals will grow (Ostwald ripening), until there is only one crystal left. The size of that crystal will be such that the concentration of the supernatant will be given by the point on curve ABC which will give mass balance.

This is not reasonable, but it is difficult to disprove, because the time it would take, were it true, would be so long that it could not be carried out.

In solubility work, it is conventional to require 72 h for equilibrium to be attained. One might invoke criteria such as that if one tested the concentration every 24 h, solubility had been reached when there was no “detectable” increase in solubility. But this is no guarantee that the concentrations over a 6-month period would not increase; or would decrease, if the crystals grew and the equation were correct.

It is possible, indeed very possible, that the basic equation [Eq. (6.2)] is incomplete. For instance there is no accounting for defect formation, and the interfacial energy is simply assumed to be proportional to some “size.” It is more logical to think that the real equation would be one leading to a curve as shown in Fig. 6.3.

At $r > 0$ Fig. 6.3 may be approximated by a Morse-type curve:

$$\ln[C_s] = (\beta/r) - (\phi/r^2) \quad (6.10)$$

where ϕ is a constant and where

$$\beta = \{(MW)6\sigma/\rho\}/(RT) \quad (6.11)$$

If, when r is large, $(\beta/r) \gg (\phi/r^2)$, then the equation reduces to

$$\ln[C_s] = \beta(1/r) \quad (6.12)$$

so

$$r = \beta / \ln[C_s] \quad (6.13)$$

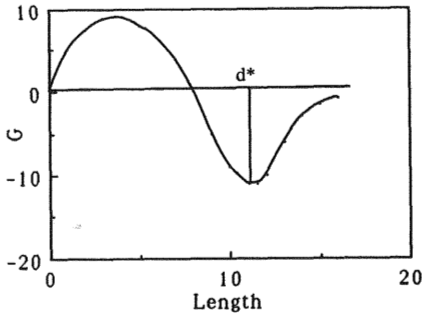


Fig. 6.3 Modified model of chemical potential as a function of size.

6.5. HOMOGENEOUS NUCLEATION

The work required to create a nucleus of size d , is given by

$$W = 6d^2\sigma \tag{6.14}$$

It is seen from this that if a solution is supersaturated to a degree of $S = C/C_2(\geq 1)$, then

$$\ln[S] = 6(MW\sigma/RT\rho)(1/d) \tag{6.15}$$

or

$$d = 6(MW\sigma/(RT\rho\ln[S])) \tag{6.16}$$

Inserting Eq. (6.14) into (6.15) gives

$$W = 36\{(MW\sigma/(RT\rho\ln[S]))\} \tag{6.17}$$

Here, S is the supersaturation ratio, and it shows when this is unity, $\ln[S]$ is 0 (i.e., infinite work is required to form a nucleus). The higher the supersaturation ratio is, the more easily a nucleus will form.

Mullin (1961) reports the following times (Table 6.1) for a nucleus to spontaneously form in supercooled water vapor.

Table 6.1 Time Required for Nucleation to Take Place

Supersaturation ratio	Time
1	Infinite
2	10^{62} yr
3	10^3 yr
4	0.1 s
5	10^{-13} s

Source: Mullin (1961).

6.6. EFFECTS OF IMPURITIES

Impurities in the intermediate drug substance are usually removed by recrystallization. It is assumed in calculations that if the impurity is higher than its solubility limit at the conditions of precipitation of the drug substance, then it is "removed," in that it stays in solution.

However incorporation (doping) of solids by introducing guest molecules into the host lattice is possible, and this often happens. Figure 6.4 is an example of this. There appears to be an asymptotic limit to the uptake (in this case, 0.005 mol fraction).

The inclusion also affects the ability of the crystal to contain water (up to a certain point). Because (as in the previously cited case) the inclusion leads to lattice vacancies, the "space" created presumably allows "room" for the water molecules.

6.7. YIELD AND METASTABLE ZONES

Chow et al. (1985) studied the effect of additives in the mother liquor on the outcomes of crystallization. One effect is on the yield, and this may be an important consideration, because only relative small amounts of additive (impurity) may affect a great number of properties of the crystallization and the crystals (Fig. 6.5).

At first sight it might be speculated that acetoxyacetanilide increases the solubility of acetaminophen, but even though this is true, the extent of solubility increase (about 6% at the highest concentration of additive) does not explain the dramatic decrease in yield, and the explanation lies in an expansion of the metastable zone.

With homogeneous nucleation there is often a lag time before crystallization starts. In the foregoing example, Chow reported that without seeding and the presence of acetoxyacetanilide the system did not start crystallizing in 2 h.

An example of homogeneous nucleation is suspensions of amorphous frusemide (furosemide). The amorphous state is much more energetic (more soluble) than any of the crystalline states, and in a suspension of amorphous furosemide, Doherty and York (1987) report the following crystallization profile (Fig. 6.6).

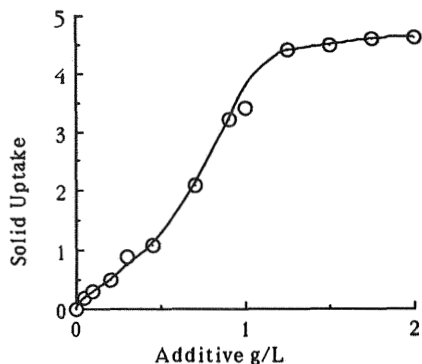


Fig. 6.4 The solids uptake is in units of mol fraction $\times 10^3$. (Data from Chow et al., 1985.)

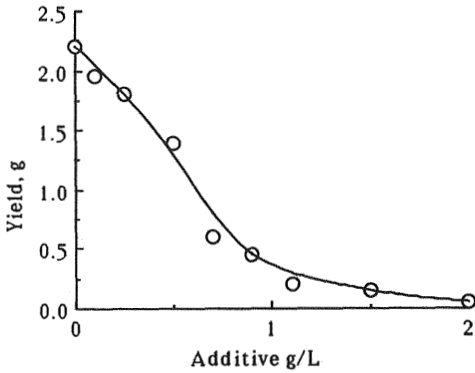


Fig. 6.5 The effect of *p*-acetoxyacetanilide on the yield of acetaminophen at 30°C. The solution originally contained 9 g of acetaminophen per 390 cm³ of water.

The decrease in concentration (*C*) follows a curve of the type

$$C - C_s = (C_0 - C_s)e^{-qt} \quad (6.18)$$

But it should be noted that *q* is neither a growth nor a nucleation rate constant.

6.8. CRYSTAL GROWTH

A diffusion theory of crystallization, also used in early dissolution work, was first suggested by Noyes and Whitney (1897a,b). They also assumed that dissolution was the reverse of crystallization, and that the crystallization and dissolution rates were the same. Reference is made to Fig. 6.7, where a film at the crystal surface exists. According to Noyes and Nernst, for diffusion

$$dM/dt = k_d A(C_1 - C_2) \quad (6.19)$$

where *C*₂ is solubility. Berthoud and Valetton have shown that a reaction term must be included:

$$dM/dt = k_r A(C_2 - C_3) \quad (6.20)$$

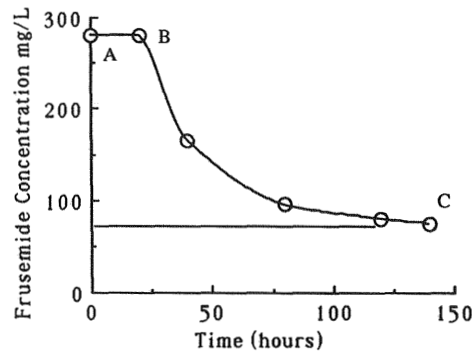


Fig. 6.6 Crystallization of a 16% amorphous furoseamide (frusemide) suspension. (Data from Doherty and York, 1987.)

where $C_3 > C_s$. In general

$$dM/dt = KA(C_1 - C_3) \quad (6.21)$$

where, as shall be discussed shortly

$$(1/K) = (1/k_d) + (1/k_r) \quad (6.22)$$

where k_r is a "reaction constant" and k_d is the diffusion constant. The reason for the expression in Eq. (6.22) is that if the film were stagnant, then (Mullin, 1960)

$$k_d = D/h \quad (6.23)$$

But it stands to reason that the film thickness would have to depend on the agitation speed, and Marc (1908), indeed, found h to be zero at high velocities. This would imply an infinite growth rate at high liquid velocity. A model overcoming this problem was proposed by Berthoud (1912) and Valetton (1924), who suggested that there were two processes, one a dislodging of molecules from the surface (the so-called reaction rate k_r , referred to in the foregoing), and the second being the diffusion as discussed in the foregoing.

Higbie (1935) and Dankwerts (1951) suggested a surface renewal theory where, simply

$$k_d = (Df)^{1/2} \quad (6.24)$$

f is, here, the fraction rate of surface renewal.

6.9. LOG-LOG SIZE DISTRIBUTIONS AFTER HOMOGENEOUS NUCLEATION

If a metastable polymorph is allowed to dissolve, as shown in a previous chapter, then it will approach a higher solubility number than a more stable form. In Fig. 6.8, the metastable form would approach a concentration of $C_1 = 200$ mg/g if no conversion took place. However, at a given point in time (10 time units), precipitation starts, and it often happens that in a time period (20–40 time units in the figure), the concentration stays constant. At a point B, all the metastable material in steady-state discontinues and the concentration decreases toward the saturation concentration C_2 of the more stable polymorph.

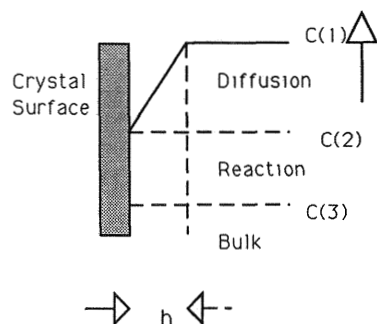


Fig. 6.7 Schematic of concentration profile at a crystal-supersaturated solution interface.

The steady-state phenomenon happens because the rate at which a suspended metastable drug substance dissolves ($-k_1(C_1 - C)$) equals the rate with which the stable form precipitates ($-k_2(C - C_2)$). C_{steady} is given by

$$[-k_1(C_1 - C_{\text{steady}})] = [-k_2(C_{\text{steady}} - C_2)] \quad (6.25)$$

that is,

$$C_{\text{steady}} = \{k_1 C_1 - k_2 C_2\} / (k_1 - k_2) \quad (6.26)$$

The steady-state is actually never quite accomplished, but the fact remains that there is a region AB where the concentration is fairly constant.

Under such conditions, the nucleation and growth rates of the crystals are constant (Fig. 6.8)

This situation is an oversimplified model for general crystallizations, but serves well as an introduction into how distributions are arrived at. The question that poses itself first is, what is the rate of nucleation? We will see shortly that, most often, it is dependent on the degree of supersaturation, but in the foregoing situation the degree of supersaturation (between A and B) would be constant. We will assume, for the moment, that a crystallization event in the range AB takes T time units, and that n nuclei are formed each time unit, that is,

$$dn/dt = q \quad (6.27)$$

Growth rates are also a function of supersaturation, but in AB this is constant and it will also be assumed that the growth of the size, a , follows MacCabe's law:

$$da/dt = k \quad (6.28)$$

These are obviously severe assumptions for a general case, but they introduce us to the manner in which crystallization events are translated into particle size distributions of the ensuing product.

Assume, first, that the T time units are divided into intervals, each of 1 time unit. Then there will be n nuclei that will have grown for T time units, n that have grown for $T - 1$ time units and so on.

The crystal that was born in the first time interval will have the size:

$$a_0 = kT^3 \quad (6.29)$$

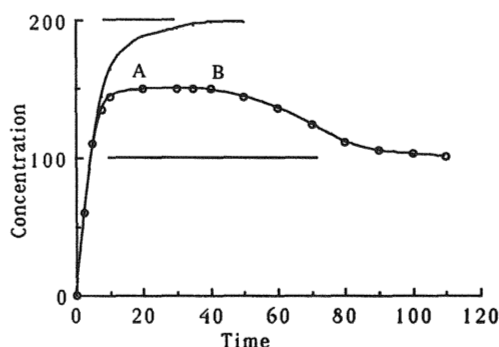


Fig. 6.8 Concentration-precipitation time curve. (Data from Doherty and York, 1987.)

The one born in the second time interval will have the size

$$a_1 = k(T - 1)^3 \quad (6.30)$$

so that the total weight of the crystals will be

$$W = \rho kn \{T^3 + (T - 1)^3 + \dots (2^3 + 1^3)\} \quad (6.31)$$

Because the time unit is one, the sum of the series equals the integral:

$$W = \rho kn \int_0^T T^3 dT = \rho kn T^4 / 4 \quad (6.32)$$

If one considers the amount of material that has sources from times 0 to t , then this would be

$$W = \rho kn \{T^3 + (T - 1)^3 + \dots (T - t)^3\} \quad (6.33)$$

This material will have sizes at or above

$$a^* = k(T - t) \quad (6.34)$$

The sum in Eq. (6.33) is equal to

$$W = \rho kn \int_0^{T-t} T^3 dT = \rho kn (T - t)^4 / 4 \quad (6.35)$$

so that the weight fraction $f(> a^*)$ of material with a particle size larger than a^* is

$$f(> a^*) = (T - t)^4 / T^4 \quad (6.36)$$

or by taking logarithms

$$\ln[f(> a^*)] = 4 \ln[(T - t)^4 / T^4] \quad (6.37)$$

But

$$(T - t)^4 / T^4 = a^* / a_{\max} \quad (6.38)$$

so that

$$\ln[f(> a^*)] = 4 \ln[a^* / a_{\max}] \quad (6.39)$$

Hence, plotting the weight frequency of particles larger than a^* versus the logarithm of the size should give a straight-line with slope 4.

The data by Otsuda and Matsuda (1998), however, unlike what their article might suggest, is not necessarily log-log. If the data points are taken off their Fig. 1 (as well as it may be carried out), the distribution looks as shown in Table 6.2 and Fig. 6.5 and Fig. 6.6.

The data are treated in Table 6.2 to allow plotting according to either a normal or a lognormal distribution. As shown in Fig. 6.9 the distribution, if simply judged visually, could be either, but Fig. 6.10 (plotted from data in Table 6.2) shows it to be lognormal.

The geometric mean is seen to be given by

$$\ln[a_{gw}] = 7.4373 / 1.505 = 4.97 \quad (6.40)$$

that is,

Table 6.2 Example of Lognormal Calculation

Size (d)	Undersized (%)	Z-value	ln[d]
20	0.2	-2.880	2.996
30	1.1	-2.190	3.401
40	3	-1.880	3.689
50	5.5	-1.600	3.912
60	9	-1.340	4.094
70	15	-1.045	4.248
80	20	-0.840	4.382
90	25	-0.670	4.500
125	45	-0.013	4.828
150	55	0.013	5.011
200	70	0.525	5.298
220	80	0.845	5.394

Source: Otsuka and Matsuda (1998).

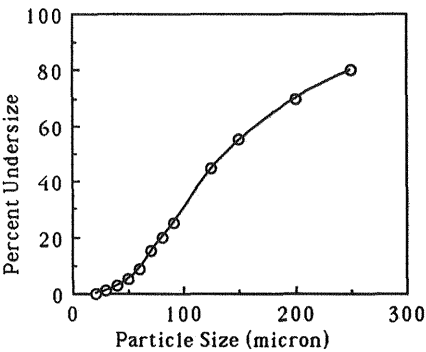


Fig. 6.9 Graph of data from Otsuka and Matsuda (1996).

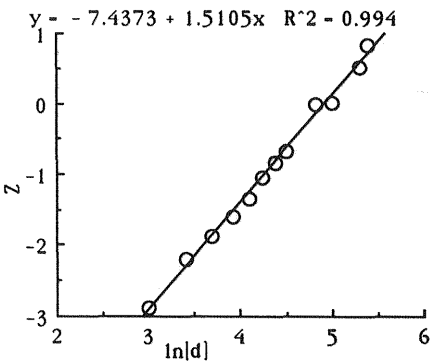


Fig. 6.10 The data in Table 6.2 treated as a lognormal distribution.

$$a_{gw} = 144 \mu\text{m} \quad (6.41)$$

This corresponds fairly well with the “mean” arrived at by Otsuka and Matsuda (1996). The standard deviation is the inverse of the slope,

$$\ln[\sigma_w] = 1/1.51 = 0.6625 \quad (6.42)$$

Knowledge of the geometric mean diameter allows calculation with the Hatch–Choate relation:

$$\ln[d_{sv}] = \ln[a_{gw}] - 0.5 \ln[\sigma_w] \quad (6.43)$$

from which

$$d_{sv} = 92 \mu\text{m} \quad (6.44)$$

It is obvious that this figure is considerably higher than the value that the authors found from BET surface measurements; therefore, it is legitimate to state that the two methods give different results. It is, however, not legitimate simply to compare a_{gw} with a_{sv} , because (as demonstrated) the higher-moment diameter is, by definition, larger for a multiparticulate.

6.10. NUCLEATION

The chemical energy ΔG associated with 1 mol transferring from a supersaturated solution of concentration C to a saturated solution (i.e., a type of situation that will occur in thermal recrystallization) is given by

$$\Delta G = -RT \ln\{C/S\} = -RT \ln[q] \quad (6.45)$$

where R is the gas constant and T is absolute temperature. C/S is denoted the supersaturation ratio and is, in the following, symbolized with the letter q :

$$q = C/S \quad (6.46)$$

Because S represents the concentration in a solution in equilibrium with the solid state, Eq. (6.45) represents the energy of transfer of one mole from solution to the crystalline state. For crystallization to occur, there must be a nucleus from which the crystal(s) grows. The rate of crystallization is, therefore, in some form or manner, associated with the rate of nucleation. Denoting time with the symbol ϕ and the number of nuclei at any given time by N , the rate may be expressed as $dN/d\phi$. Furthermore, Eq. (6.2) represents the energy of activation for nucleation. The nucleation rate, J , is given by

$$J = dN/d\phi = J_0 \exp(-RT \ln\{C/S\}) = J_0 \exp(-\ln[q]) = J_0 q^{1/n} \quad (6.47)$$

Most often this is associated with an exponent $1/n$, so that the expression, if $C \gg S$, becomes

$$J = \alpha(C - S)^{1/n} \quad (6.48)$$

Frequently the value of n is 2 (i.e., $1/n = 1/2$). In the writing to follow the aim is to deduce what type of particle size distribution would result from thermal recrystallization.

6.11. TEMPERATURE AND SOLUBILITY PROFILES DURING THERMAL RECRYSTALLIZATION

In thermal recrystallization, excess drug is dissolved in solvent at a higher temperature at which its solubility is more than its ambient solubility, and the temperature is then allowed to drop by cooling, either natural or induced. The question is: What would the solubilities of the compound be as a function of cooling time?

Heat transfer usually results in temperatures following a sigma-minus function, that is,

$$T = T_0[1 - \exp(-k\phi)] \quad (6.49)$$

An example of this when the ambient temperature is 23°C, the starting temperature is 40°C, and the harvesting temperature is 25°C, is shown in Fig. 6.11.

If the solubility of a compound is assumed to follow a van't Hoff equation, then

$$\ln[S] = (-\Delta H/RT) + \beta \quad (6.50)$$

where β is a constant and ΔH is the heat of solution.

Combining Eqs. (6.49) and (6.50) would then give the temperature as a function of time. Rather than arriving at the complex relations that would arise from this, an approximation approach has been taken as shown in the following example:

Example 6.1

Suppose a recrystallization takes place and the temperature is at 40°C at time 0 and at 25° at time 10. Assume the ambient (or cooling) temperature is 23°C. Assume the solubilities at 40°C is 50 and at 25°C is 30. Draw the temperature versus time and the solubility versus time curves.

Answer 6.1

In the stated case, Eq. (6.49) would take the form:

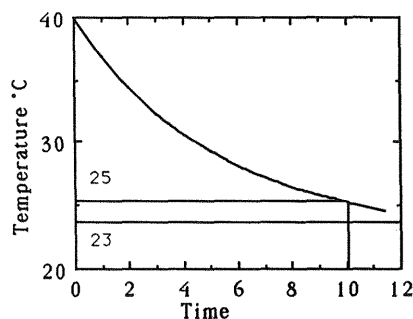


Fig. 6.11 Cooling curve starting at 40°C toward ambient temperature of 23°C. Recrystallization is stopped at 25°C.

$$T = 23 + (40 - 23)(1 - \exp(-k\phi)) \quad (6.51)$$

or, since at $\phi = 10$, $T = 25$:

$$25 = 23 + 17(1 - \exp(-k\phi)) \quad (6.52)$$

from which

$$k = 0.2 \quad (6.53)$$

The curve $T = 23 + 17(1 - \exp(-0.2\phi))$ is shown in Fig. 6.11.

Again assuming a van't Hoff equation to hold then, given the solubility of the compound to be recrystallized is 50 at 40°C and 30 at 25°C then it is easily calculated that the solubility would be a function of temperature by way of

$$\ln[S] = (-3163.5/T) + 14.014 \quad (6.54)$$

This is now converted to solubility versus time, most easily by programming (e.g., as the program in BASIC; Tables 6.3 and 6.4).

The temperature versus time curve is shown in Fig. 6.11. The solubility versus time curve is shown in logarithmic fashion in Fig. 6.12, and the curve is a logarithmic decay by way of Eq. (6.55):

$$\ln[C - S(23)] = 3.05 - 0.23\phi \quad (6.55)$$

$C - S(23)$ is the supersaturation and is given by

$$C - S(23) = 21.6 \exp(-0.23\phi) \quad (6.56)$$

6.12. PARTICLE SIZE DISTRIBUTION AFTER THERMAL RECRYSTALLIZATION

From the example it is seen that it is reasonable to assume that the *supersaturation* as a function of time may be given by

$$\Delta = (C_0 - S) \exp(-k\phi) \quad (6.57)$$

where C_0 is the concentration at the beginning temperature and S is the solubility at the ambient temperature.

Rates of growth may frequently be expressed as

$$dm/d\phi = MA\Delta^g \quad (6.58)$$

where A is the surface area, and M is a growth rate constant and g is an exponent, usually of value close to 2.

Table 6.3 Program for Generating Values by Way of Eq. (6.51)

```

For T1 = 0 to 10
T2 = 23 + 17*EXP(-0.2*T)
S1 = -3163.5/(T2 + 273.15)
S2 = S1 + 14.014
S3 = EXP(S2)
PRINT T1, T2, S3
NEXT T1

```

Table 6.4 Printout of Data Generated in Table 6.3

Time	Temperature	Solubility
0	40	49.4
1	36.9	44.7
2	34.4	41.1
3	32.3	38.3
4	30.6	36.2
5	29.3	34.5
6	28.1	33.2
7	27.2	32.1
8	26.4	31.3
9	25.8	30.6
10	25	30.0

The mass of one single cubic particle, with side length r , is

$$m = r^3 \rho \tag{6.59}$$

so that

$$dm/d\phi = 3r^2 \rho (dr/d\phi) \tag{6.60}$$

The area A of the surface of the cube is

$$A = 6r^2 \tag{6.61}$$

Eqs. (6.60) and (6.61) now give

$$dm/d\phi = 3r^2 \rho (dr/d\phi) = M6r^2 \Delta g \exp(-gk\phi) \tag{6.62}$$

or

$$dr/d\phi = (2M/\rho) \Delta g \exp(-gk\phi) \tag{6.63}$$

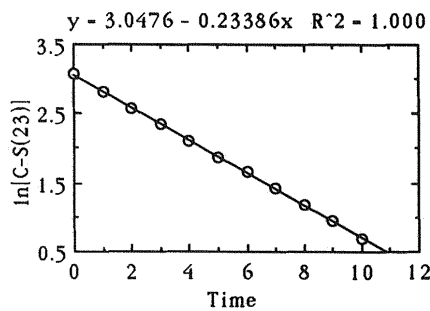


Fig. 6.12 Concentration less saturation concentration at 23°C plotted in a semilogarithmic fashion versus time.

The length of time given to the crystallization is denoted τ . The size of a particle that is born at time ϕ is given by:

$$r_\phi = (2M/\rho)\Delta g \int_\phi^\tau \exp(-gk\phi) d\phi = (2M/\rho)\Delta g [e^{-gk\phi} - e^{-gk\tau}] \quad (6.64)$$

The size of the largest particle r_0 is obtained by inserting $\phi = 0$ in this equation:

$$r_0 = (2M/\rho)\Delta g [1 - e^{-gk\tau}] \quad (6.65)$$

The number of particles that are born between time ϕ and $d\phi$ is given by:

$$J = dN/d\phi = \alpha[(C(\phi) - S)]^{1/n} = \alpha\Delta^{1/n} \exp(-k\phi/n) \quad (6.66)$$

The total number of particles is obtained by integrating this from 0 to τ

$$N = \alpha\Delta^{1/n} \int_0^\tau \exp(-k\phi/n) d\phi = \alpha\Delta^{1/n} \{1 - e^{-k\tau/n}\} \quad (6.67)$$

By the same argument, the number of particles with particle size larger than r_ϕ is denoted $N_{>}$ and is given by integration of the integral in Eq. (6.67) from ϕ to τ :

$$N_{>r(\phi)} = \alpha\Delta^{1/n} \{e^{-k\phi/n} - e^{-k\tau/n}\} \quad (6.68)$$

Equation (6.64) may be written

$$[e^{-gk\phi}] = [\rho r_\phi / (2M\Delta g)] + e^{-gk\tau} \quad (6.69)$$

Inserting this in Eq. (6.68) now gives

$$N_{>r(\phi)} = \alpha\Delta^{1/n} \left\{ \left[\rho r_\phi / (2M\Delta g) \right] + e^{-gk\tau} \right\} - e^{-k\tau/n} \quad (6.70)$$

which, when the symbol r is substituted for $r(\phi)$ is the cumulative distribution function, (Eq. (6.70) divided by Eq. (6.67)).

Carstensen (1980) and Rodriquez (1985) have shown that these functions, for $n = 1/2$ and $g = 2$, resemble lognormal distribution functions.

6.13. HETEROGENEOUS NUCLEATION

As mentioned in the foregoing, there is often a lag time before nucleation starts. This, in some ways, is tied in with the metastable zone.

It is customary to seed a crystallization with seeds of the drug substance. This may eliminate the lag time and, often, reduces the energy of activation for the critical nucleus formation (i.e., ΔG in Fig. 6.2).

6.14. CRYSTAL HABIT

Once a nucleus is formed at or beyond the critical size it will continue to grow. It can either grow equally rapidly in all directions (situation i in Fig. 6.13), or the growth may be impaired in one direction (see ii in Fig. 6.13), in which case a plate results. If the growth is impaired in two directions, then a needle results (see situation iii in Fig. 6.13).

The drug substance, per se, may be such that one of the three situations is preferred. There are some compounds that always crystallize out as needles.

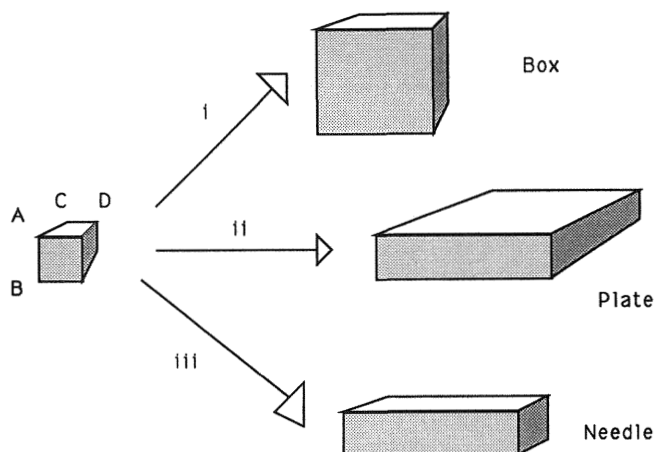


Fig. 6.13 Creation of different crystal habits from a nucleus. (i) all directional growth rates are equal; (ii) one directional growth rate is lower than the other two; (iii) two directional growth rates are lower than the third.

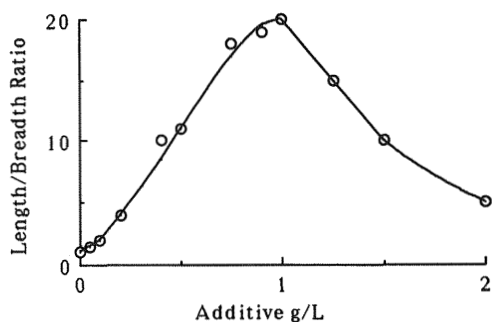


Fig. 6.14 Modification of acetaminophen crystals: influence of growth in aqueous solution containing *p*-acetoxyacetanilide on crystal properties. (Data from Chow et al., 1985.)

However, additives affect the dimensions in the crystallization of certain substances. Figure 6.14 shows the results from the presence of *p*-acetoxyacetanilide on the dimensions (length/breadth ratio) of acetaminophen (Chow et al., 1985).

REFERENCES

- Berthold A (1912). *J Chim Phys* 10:624.
 Bikerman JJ (1970). *Physical Surfaces*. Academic Press, New York, p 215.
 Carstensen JT (1980). *Solid Pharmaceuticals: Mechanical Properties and Rate Phenomena*. Academic Press, New York, pp 30–32.
 Carstensen JT, Rodruguez-Hornedo N (1985). *J Pharm Sci* 74:1322.
 Chow A H-L, Chow PKK, Zhognshan W, Grant DJW (1985). *Int J Pharm* 24:239–258.
 Dankwerts PV (1951). *Ind Eng Chem* 43:1460.
 Doherty C, York P (1987). *Int J Pharm* 34:197–205.

- Higbie R (1935). *Trans Am Inst Chem Eng* 31:365.
- Marc R (1908). *Z Phys Chem* 61:385.
- Mullin JW (1961). *Crystallization*. Butterworths, London, p 106.
- Noyes AA, Whitney WR (1897). *J Am Chem Soc* 19:930.
- Noyes AA, Whitney WR (1897). *Z Phys Chem* 47:689.
- Nyvlt J (1971). *Industrial Crystallisation from Solutions*. Chemical Rubber, Cleveland, OH.
- Ostwald W (1897). *Z Phys Chem* 22:289.
- Otsuka N, Matsuda Y (1996). *J Pharm Sci* 85:112.
- Valeton JJP (1923). *Z Kristallogr* 59:135; 335.

Amorphates

7.1. Methods of Preparation	108
7.2. Amorphates	109
7.3. Glass Transition Temperatures of Mixtures	109
7.4. Use of Modulated Differential Scanning Calorimetry	110
7.5. Water Absorption “Isotherms” into Amorphates	110
7.6. Experimental Determination of Amorphates	112
7.7. Crystallization of Amorphates	112
7.8. Polymers	114
Symbols	115
References	115

It was previously mentioned that *amorphates* are simply defined as materials that are not crystalline. In general, they are more energetic (less stable) than any crystalline form, although there have been some exceptions reported in the literature. Because of this they have higher dissolution rates and apparent solubilities (Buckton and Beezer, 1992; Ahmed et al., 1998), stability (Carstensen and Morris, 1993; Carstensen et al., 1993; Pikal, 1978).

At times materials are produced in amorphous form by methods usually used for producing crystalline modifications. Recrystallization from different solvents is not always successful. Chow and Grant (1988, 1989) have described that recrystallization of acetaminophen from a series of solvents gave rise to amorphous material and different crystal forms.

The theory of Volmer and Weber–Becker and Doring (the VWBD-theory) states that crystals form as a function of cluster formation (of volume v) of supersaturation S ; as an end result, the nucleation rate J is a function of interfacial tension σ between solid and liquid by the following formula:

$$J = \exp\{-16\pi\sigma^3 v^3 N / \{3R^3 T^3 (\ln S)^2\}\} \quad (7.1)$$

where N is Avogadro's number, R is the gas constant, and T is absolute temperature. The equation holds well for vapors and solutions (Mullins and Leci, 1969), but does not apply well to supersaturation situations or melts, particularly for more complex molecules.

Tamann (1926) showed that for melts there is maximum in J at a particular temperature. Turnbull and Fisher (1949) modified the VWBD equation to read:

$$J = \exp\left[\left\{-16\pi\sigma^3 v^3 N / \{3R^3 T^3 (\ln S)^2\}\right\} + \Delta G_m / RT\right] \quad (7.2)$$

where ΔG_m is activation energy for motion of molecules across the matrix-cluster interface. ΔG_m is highly dependent on the viscosity of the melt.

It is obvious, therefore, that certain substances that possess high viscosity at their melting point may be prone to become amorphous on melting and recooling

7.1. METHODS OF PREPARATION

At times it is actually difficult to prepare an organic compound in crystalline form, and in such a case, the problem lies in producing the crystalline substance. Mechanical interaction is often a means; it is remembered from organic laboratory courses that students will produce a dispersion in a test tube, and then scrape the side of the test tube with a spatula. In general terms, some means of nucleation must be created.

Hildebrand and Müller-Goymann (1967) report on the production of sodium ketoprofen by neutralization of ketoprofen with sodium hydroxide. Both methanol and water as solvents produce a hygroscopic glass. However, if this glass is suspended in 95% ethanol and stirred at length, a crystalline sodium salt will eventually occur.

The opposite, to create a substance in amorphous form when it is easily crystallized may be achieved, in general, in the following manners:

Sublimation

Supercooling of melts

Neutralization of an acid with a base (if the drug is an acid) or vice versa

Recrystallization from a variety of solvents

Dehydration of hydrates

Lyophilization (e.g., by "kugeln")

Spray-drying

To name some examples, hard candy, produced by *melting* sucrose, is amorphous. If it crystallizes during storage, then it becomes cloudy and is considered defective candy. Amoxicillin trihydrate becomes amorphous on *dehydration*. Kakkar et al. (1997) prepared three crystalline forms of ciprofloxacin HCl; furthermore, they prepared the amorphous form by *lyophilization*. Lyophilization of sucrose produces amorphous sugar and will be touched on later in the chapter. As an example of *spray-drying*, spray-dried lactose has a high amorphate content.

7.2. AMORPHATES

Solids that are not crystalline are denoted amorphous. If one melts a (stable) solid and recools it, then it should crystallize when the melting point is reached.

This requires nucleation, and nucleation propensity is a function of the viscosity of the liquid in which it occurs. Materials that are viscous about their melting point are, therefore, prone to form supercooled solutions.

At a given high viscosity (attained at or lower than the melting point), the melt will have the appearance of a solid, and this is the type of material referred to as amorphous.

Just below the melting point, the molecules will have no specific orientation, and molecular movements will be random in direction and magnitude (within the limits of the system), as opposed to a crystalline material, in which the molecules are arranged in lattices (ordered arrays) and the orientation of each molecule is set.

At a temperature T_g , lower than the melting point, there will be a physical change in the amorphate. An example of this is shown in Fig. 7.1.

Between points A and B the properties of the amorphate is often similar to that of the melt, and is referred to as the “rubbery” state, and below C it is referred to as a glass. At the glass transition temperature T_g , the viscosity of the melt is often of the magnitude of 10^{12} Pa s (Lu and Zografi, 1997), and this is the “cutoff point” between a “liquid” and a “solid.”

For lyophilized materials that produce amorphous cakes, the “collapse temperature” is essentially the temperature at which the viscosity drops below a critical viscosity (e.g., 10^{12} Pa s) that will allow the cake to deteriorate.

7.3. GLASS TRANSITION TEMPERATURES OF MIXTURES

It is often of importance to estimate the glass transition of an amorphate that has a certain water (or solvent) content. If values of T_g (T_{g1} and T_{g2}) are known at two different water contents (m_1 and m_2), then T_g at other water content may be estimated by using the Gordon–Taylor equation (Gordon and Taylor, 1952).

$$T_g = (m_1 T_{g1} + K m_2 T_{g2}) / (m_1 + K m_2) \quad (7.3)$$

where

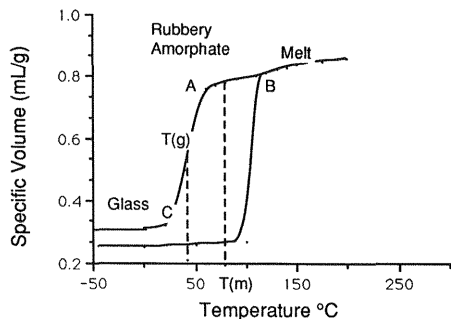


Fig. 7.1 Molecular volume as a function of temperature of a solid prone to forming an amorphate.

$$K = \rho_1 T_{g1} / \rho_2 T_{g2} \quad (7.4)$$

7.4. USE OF MODULATED DIFFERENTIAL SCANNING CALORIMETRY

This is referred to in the following as MDSC. Hill et al. (1998) have described this technique, in which rather than using a linear cooling or heating ramp, a sinusoidal temperature profile is used (Reading et al., 1993). Hill et al. (1998) investigated amorphous α -lactose and were able to measure the heat capacity at T_g separately from the endotherm.

7.5. WATER ABSORPTION “ISOTHERMS” INTO AMORPHATES

Amorphates are solids that are not crystalline. It is assumed at this point that the term *solid* is self-evident, although amorphates in the rubbery state (just below the melting point of the crystalline form of the compound) are actually highly viscous liquids. When exposed to humid atmospheres, they will pick up moisture in a fashion that is not like that of a BET isotherm (to be covered shortly). The moisture actually penetrates into the solid, and it may be considered a *solution*.

In an ideal situation, the water activity a , will decrease linearly with $(1 - x)$ where x is the molefraction of solute. At a given point ($x = 0.24$ in Fig. 7.2) the solution becomes saturated. (This concentration differs from compound to compound.) Beyond this concentration, the solution itself will be saturated, and the vapor pressure will not change with further addition of compound, rather the composition will change, but the vapor pressure will stay constant. In this type of graph the coordinates are in a direction opposite that of a usual isotherm.

If an amorphous form of the compound is produced and exposed to different relative humidities, then the isotherm is often quite linear if the amount of water absorbed is expressed as molefraction (line DE in Fig. 7.2). As shown by Carstensen and VanScoik (1989) for amorphous sugar, this line is an extension of the solution vapor pressure line (see AB in Fig. 7.2), and one may consider the moist amorphate as a highly concentrated, supersaturated “solution.”

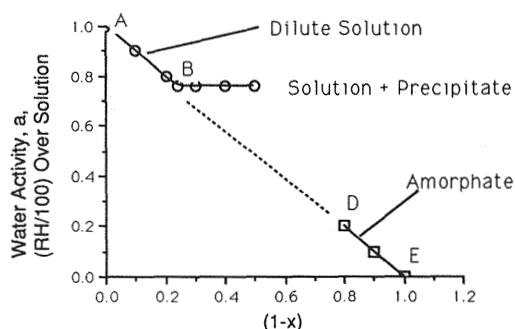


Fig. 7.2 Moisture isotherm for an amorphous solid. (Data from Carstensen and VanScoik, 1988.)

Because of the random arrangement and the mobility of the molecules in an amorphate, as opposed to a crystalline modification, amorphates are usually chemically less stable than crystalline modifications (Carstensen et al., 1993).

Carstensen and VanScoik (1988) were the first to point out that for an amorphous substance, it is illogical to use the traditional moisture isotherms, because here it is probably not an adsorption, but rather, an absorption that is at play.

By exposing amorphous sucrose to various relative humidities, various moisture levels were reached. If these moisture levels were expressed as molefraction of sucrose, then the vapor pressures fell in line with the vapor pressure curve of sucrose solutions itself.

The fraction to the right of point B is the principle used for salt solutions to obtain constant relative humidity in desiccators. With electrolytes, the vapor pressure depression is larger (owing to the two or threefold number of ionic particles, over that of the molarity of the salt), and the solubilities often high, so that these are preferred for creating constant relative humidity in desiccators.

Lehto and Laine (1998), have shown moisture isotherms of cefadroxil, for amorphate, crystalline anhydrate, and hydrate. The amorphate yields an isotherm that is constantly increasing (i.e., not of the BET-type) up to a relative humidity of 82%, at which point the isotherm suddenly drops, owing to crystallization and because the crystalline phase only can handle surface adsorbed moisture (i.e., much less than the amorphous rubbery phase).

Wu et al. (1996) found that [6-fluoro-2-(2'-fluoro-1,1-biphenyl-4-yl)-3-methyl]4-quinolinecarboxylic acid sodium salt (brequinar sodium) exists either as an amorphous form or as a hemihydrate. When it is exposed to 75% RH it absorbs water rapidly and changes into the hemihydrate. Both forms are quite water-soluble.

Hancock and Zografi (1993) later used this principle in their investigation of whether solution theory could be applied to macromolecules. To quote "If one considers the absorption process to be completely analogous to the solution process, then it should be possible to use basic solution theories to model the data..." Their data for polyvinylpyrrolidone (PVP) K30 are shown in Fig. 7.3.

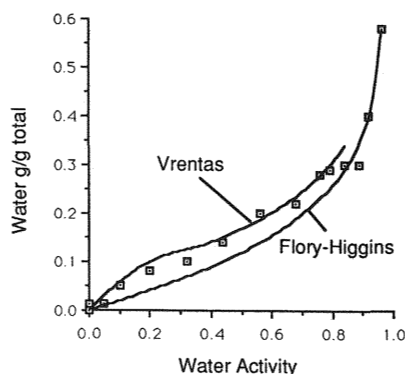


Fig. 7.3 Fit of vapor pressure data of aqueous solutions of PVP K30 at 30°C to the Flory-Huggins equation. (Data from Hancock and Zografi, 1993.) The points are taken from their Fig. 6 and Fig. 7 as accurately as possible, as is the trace of the Flory-Huggins equation.

The important feature in Fig. 7.3 is that the data fit neither the Flory–Huggins, nor the Vrentas equation. The Vrentas equation probably provides a better fit, but the adherence at activities above 0.9 are not shown; in any event, data become slightly uncertain at such high humidities.

7.6. EXPERIMENTAL DETERMINATION OF AMORPHATES

Traditionally, the fraction of a solid that is amorphous has been determined by means of X-ray diffraction. Black and Lovering, (1977) determined the fraction crystallinity in samples of digoxin powder, and Junginger (1977) determined the degree of phase transformation in this manner. Bernabei et al. (1983) have investigated the effect that crystallinity has on the enzymatic hydrolysis of the palmitate of chloramphenicol, and Ryan (1986) optimized crystallinity of lyophilizates this way. Amorphous materials, as shown by Carstensen and Morris (1989), are less chemically stable than their crystalline counterparts, as also shown by Imaizini et al. (1980) and by Gubskaya et al. (1995).

Microcalorimetry has been a useful tool in the detection of minor contents of amorphous material caused by, for instance, milling (Briggner et al., 1994; Sebhatu et al., 1994; Buckton et al., 1995; Ahmed et al., 1996), and contents of as little as 1% can be determined, which is better than determination by X-ray diffraction.

Phillips (1997) has described a means of estimation the content of amorphate in pharmaceutical powders by means of calorimetry. It is based on comparing the size of enthalpic changes in fusion and crystallization. However, because melting and crystallization occur at different points (Hancock, 1998), enthalpies are subjected to a correction to bring them to “the same temperature” by a method forwarded by Hoffmann (1958). Hancock (1998) has cautioned that there are several shortcomings of this method; for one, it is difficult to obtain a sufficiently, crystallographically pure, sample to compare the test sample against. Also, events such as transitions and desolvations, may occur in the same temperature range as melting (Ford and Timmins, 1989).

Stubberud and Forbes (1998) used microgravimetric method (CISORP Automated Sorption Monitor), to study the crystallization of amorphous lactose. They found PVP to act as an internal desiccant and delay the onset of crystallization, but many nonhygroscopic tablet excipients accelerate it.

Cases often exist in which a drug substance or excipient is partially crystalline and partially amorphous. In such cases, the quantitative content of amorphous component may be obtained by microcalorimetry. Density measurements may also be used. Densities of amorphous materials (ρ_a) are most often less than those (ρ_c) of crystalline solids, so that the content f of amorphous component may be assessed from

$$f = \rho_c / (\rho_c + \rho_a) \quad (7.5)$$

7.7 CRYSTALLIZATION OF AMORPHATES

The most common method of measuring the transformation of the metastable amorphate to more stable crystalline forms is by way of X-ray diffraction. However,

crystalline content as high as 10% may go undetected by this method (Ahmed et al., 1998; Saleki-Gerhardt et al., 1994).

The kinetics of transformation has been discussed by several authors. Ahmed et al., (1998) employ first-order kinetics in the transformation of amorphous to crystalline griseofulvin.

Carstensen and VanScoik (1989, 1990) employed weight gain (Fig. 7.4) as a means of studying the conversion of amorphous sucrose into crystalline sucrose.

They produced amorphous sugar spheres by pipetting sucrose solutions into liquid nitrogen (so-called kugeln), and lyophilizing them on petri dishes in a fashion such that no sphere touched another sphere. After freeze-drying, the petri dishes were exposed to different relative humidities and temperatures, and the weight checked as a function of exposure time. The first event that occurs is a contraction of the spheres in size, presumably owing to a change from rubbery to glassy state. The glass transition temperature is a function of moisture content, and as this increases, apparently T_g decreases, so that the transition is facilitated. This is point A in Fig. 7.4. A plateau is then reached, and at a certain given time, corresponding to B, the sucrose will begin crystallizing. The crystals cannot "hold" water in the same fashion that the amorphous phase can, so that the weight drops, and the weight drops until all the sucrose has crystallized.

The weight gain at a certain relative humidity, traditionally, would be part of an isotherm, but these isotherms are not of the conventional type, but rather, such that the amorphous, moist state behaves similar to a "solution" (i.e., a very concentrated, supersaturated solution of sucrose in water).

As seen in Fig. 7.5, the vapor pressure curve is in line with the vapor pressure curve of sucrose at less than saturation. Hence, it is logical to view this amorphous state as a supersaturated solution.

Carstensen and VanScoik found the points after the drop in weight (see phase CD Fig. 7.4) to follow a probit function. The levels, themselves (AB) may, as mentioned, be considered solubility, and as such should follow a van't Hoff plot, as they indeed do (Fig. 7.6). The plot is plotted as the plateau level, which is the inverse of the solubility and, hence, the plot has a positive slope.

Microcalorimetric methods have also been used to study amorphous to crystalline transformations (Hansen et al., 1996a,b; Angberg et al., 1991a,b, 1992a,b).

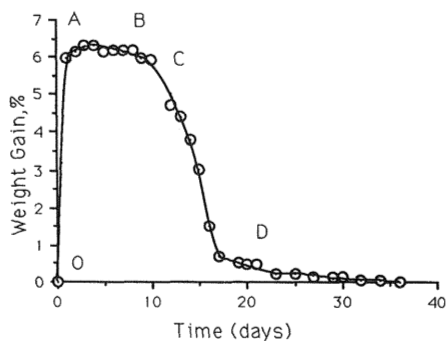


Fig. 7.4 Weight gain at 23°C and 33% RH.

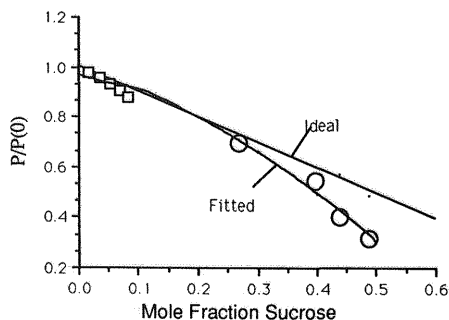


Fig. 7.5 Squares are crystalline solubilities (From *International Critical Tables*), circles are amorphous.

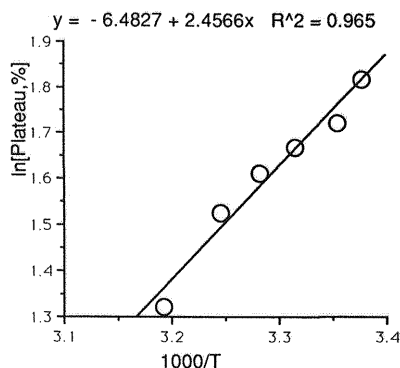


Fig. 7.6 Van't Hoff plot of plateau levels in moisture uptake by amorphates.

Angberg et al. (1991a,b) employed the method to study the transformation of amorphous lactose into the crystalline hydrate. Larsen et al. (1997), also employing this method, showed that amorphous acadesine crystallizes by way of a metastable hydrate. This decomposes very rapidly into the anhydrate.

Transformations may also be tested by way of dissolution. As is true with metastable polymorphs, concentrations will first rise to a high level (the apparent solubility of the amorphate), or approach it, but on nucleation, precipitation will occur, and the concentration will decrease to the level of the solubility of a crystalline form.

7.8. POLYMERS

Polymers will be the subject of Chapter 26 and constitute a special case of pharmaceutical solids. The aspect of amorphicity is, here, of great importance. The rubbery state confers elasticity to the polymer film, so it is important that T_g be as low as possible. Plasticizers are added to polymers to achieve this, and one means of assessing the effectiveness of a plasticizer is to record the glass transition temperature as a function of plasticizer content.

For water-soluble polymers, water is most often a good plasticizer. Water in soft gelatin capsules is controlled to within close limits. Above a critical limit the capsule will become too soft and deform in the bottle. Below a critical limit the capsules will become brittle.

The same holds true for wet granulations. Compressibility of tablets made from granulations is a function of the moisture content, and often, this is due to the elasticity of the bonding bridge of the binder that keeps the particles together. If it deforms easily, then a compressed mass is easily formed. If the granulation is overdried, then it becomes brittle and shatters during comminution, giving rise to large amounts of fines which, in turn, impedes the compression process.

Polyvinyl pyrrolidone (PVP) is a frequently used binder, and Oksanen and Zografi (1990) have shown that the glass transition temperature of PVP is strongly dependent on moisture content. If it rises above room temperature, then the polymer will be in the glassy state at the time of grinding, will be brittle, and high fines production will result.

SYMBOLS

f = fraction of amorphate in a batch of drug or excipient

G_m = Gibbs' energy for transport of a mole from cluster to solution

J = nucleation rate

m_1 = mass of amorphous component 1 in a mixture of amorphates

m_2 = mass of amorphous component 2 in a mixture of amorphates

N = Avogadro's number

PVP = polyvinylpyrrolidone

S = supersaturation

T = absolute temperature

T_g = glass transition temperature

T_{g1} = glass transition temperature of component 1 in a mixture

T_{g2} = glass transition temperature of component 2 in a mixture

K = weighted ratio constant in a mixture of amorphates

ρ_a = density of amorphous phase in a mixture of amorphous and crystalline phase

ρ_c = density of crystalline phase in a mixture of amorphous and crystalline phase

ρ_1 = density of component 1 in a mixture of amorphates

ρ_2 = density of component 2 in a mixture of amorphates

v = cluster volume

σ = interfacial tension

REFERENCES

- Ahmed H, Buckton G, Rawlins DA (1996). *Int J Pharm* 130:195.
 Ahmed H, Buckton G, Rawlins DA (1998). *Int J Pharm* 167:139.
 Angberg M, Nyström C, Castensson S (1991a). *Int J Pharm* 73:209.
 Angberg M, Nyström C, Castensson S (1991b). *Int J Pharm* 77:269.
 Angberg M, Nyström C, Castensson S (1992a). *Int J Pharm* 81:153.
 Angberg M, Nyström C, Castensson S (1992b). *Int J Pharm* 83:11.

- Becker R, Doring W (1935). *Ann Physik* 24:719.
- Bernabei MT, Forni F, Coppi G, Iannucelli V, Cameroni R (1983). *Farm Ed Prat* 38:391.
- Black DB, Lovering EG (1988). *J Pharm Pharmacol* 29:634.
- Briggner L-E, Bucton G, Byström K, Darcy P (1994). *Int J Pharm* 105:125.
- Buckton G, Beezer AE (1992). *Int J Pharm* 82:R7-10.
- Buckton G, Darcy P, Greenleaf D, Holbrook P (1995). *Int J Pharm* 116:113.
- Carstensen JT, Morris T (1993). *J Pharm Sci* 82:657.
- Carstensen JT, Franchini M, Pudipeddi M, Morris T (1993). *Drug Dev Ind Pharm* 19:1811.
- Chow AH, Grant DJW (1988). *Int J Pharm* 51:115.
- Chow AH, Grant DJW (1989). *Int J Pharm* 52:123.
- Ford JJ, Timmins P (1989). *Pharmaceutical Thermal Analysis: Techniques and Applications*. John Wiley & Sons, New York.
- Gordon M, Taylor JS (1952). *J Appl Chem* 2:428.
- Gubskaya AV, Lisnyak YV, Blagoy YP (1995). *Drug Dev Ind Pharm* 21:1953.
- Hildebrand GE, Müller-Goymann CC (1997). *J Pharm Sci* 86:854.
- Hancock BC (1998). *Int J Pharm* 160:131.
- Hansen LD, Crawford JW, Keiser DR, Wood RW (1996a). *Int J Pharm* 135:31.
- Hansen LD, Pyne MT, Wood RW (1996b). *Int J Pharm* 137:1.
- Hill VL, Craig DQM, Feely LC (1998). *Int J Pharm* 161:93.
- Hoffmann JD (1958). *J Chem Phys* 29:1192.
- Imaizini H, Nambu N, Nagai T (1980). *Chem Pharm Bull* 28:2565.
- Junginger H (1977). *Dtsch Apoth Ztg* 117:456.
- Kakkhar AP, Singh M, Mendiratta A (1997). *Drug Dev Ind Pharm* 23:1063.
- Larsen MJ, Hemming DJB, Bergstrom RG, Wood RW, Hansen LD (1997). *Int J Pharm* 154:103.
- Lehto E, Laine E (1998). *Int J Pharm* 163:198.
- Lu Q, Zografi G (1997). *J Pharm Sci* 86:1374.
- Mullins JW, Leci CL (1969). *J Cryst Growth* 5:75.
- Oksanen, CA, Zografi G (1990). *Pharm Res* 79:1374.
- Phillips EM (1997). *Int J Pharm* 149:267.
- Reading M, Elliot D and Hill VL (1993). *J Therm Anal* 40:949.
- Ryan JA (1986). *J Pharm Sci* 7:654.
- Sebhatu T, Angberg M, Ahlneck C (1994). *Int J Pharm* 104:135.
- Stubberud L, Forbes RT (1998). *Int J Pharm* 163:145.
- Tamann G (1926). *The States of Aggregation*. Mehl RF, trans. Van Norstrand, New York, p 105.
- Turnbull D, Fisher JC (1949). *J Chem Phys* 17:71.
- Vesa-Pekka L, Laine E (1998). *Int J Pharm* 163:49.
- Volmer M, Weber A (1925). *Z Physk Chem* 119:277.
- Wu L-S, Pang J, Hussain MA (1996). *Pharm Dev Technol* 1:43.

Polymorphism

8.1. Polymorphs, Methods and Detection	118
8.2. Enantiotropes and Monotropes	119
8.3. Stability of Metastable Polymorphs: The “Disappearing” Polymorph	121
8.4. Rates of Conversion in Moist Storage	123
8.5. Mixed Polymorphs	125
8.6. Pseudopolymorphism	125
8.7. Solubility and Thermodynamic Functions	126
8.8. Mixtures of Polymorphs	127
8.9. Dissolution Rates of Polymorphs and Pseudopolymorphs	128
8.10. Rates of Conversion in Moist Storage	129
Symbols	129
References	130

The pharmaceutical interest in polymorphs is attributable to the work by Aguiar et al. (1967), who demonstrated that different polymorphic forms of chloramphenicol gave not only different dissolution rates, but also distinctly different degrees of biological absorption.

Inorganic (particularly ionic) solids usually are associated with one and only one crystal system. Well-known to all is that sodium chloride is cubic.

Organic solids, however, depending on how they are recrystallized, may occur in several different crystal modifications (polymorphs). There are two types of polymorphism, enantiotropes and monotropes. They are distinguished by their vapor pressure diagrams and differential scanning calorimetry (DSC) traces (see Figs. 8.1 through 8.4).

It may almost always be assumed that more than one polymorph exists in a new drug substance. One of the tasks of the pharmaceutical scientists is then to produce as many polymorphs as possible at the earliest time possible during the product development stages.

8.1. POLYMORPHS, METHODS AND DETECTION

Methods for (attempts at) producing different crystal forms most often take the form of recrystallization from different solvents. If the compound is heat-stable, then sublimation (e.g., Schnitzer et al., 1997) may be attempted. Giordano et al. (1998) studied crystal forms of piroxicam pivalate by recrystallization from toluene, ethyl acetate, ethyl ether, and ethanol (Table 8.1). This was done at room temperature (RT) or ice cooling (I) with (S) or without (WO) magnetic stirring. Two polymorphs (i and ii) were obtained, under the mentioned conditions.

One way of distinguishing between different polymorphs is by difference in X-ray patterns. Often, however, infrared spectra (IR) show distinct differences. Table 8.2 shows the wave numbers (reciprocal centimeters) of certain bands in the Fourier transform infrared (FTIR) spectra of the two polymorphs.

Recrystallization from different solvents is not always successful. Chow and Grant (1988, 1989) have described that recrystallization of acetaminophen from a series of solvents gave rise to amorphous material and different crystal forms, but this could not be duplicated, in the same solvents, by deVilleiers et al. (1998).

Table 8.1 Pyroxicam Pivalate Polymorphs

Solvent	RT-S	RT-WO	I-S	I-WO
Toluene	i	i	i	i
Ethyl ether	i	i	i	i
Ethyl acetate	i	i	ii	i + ii
Ethanol	i	i	i	i

Source: Giordano et al. (1998).

Table 8.2 FTIR Spectra of the Two Polymorphs

Functional group	Polymorph i	Polymorph ii
NH	3253	3291, 3350
C=O, ester	1760	1750, 1767
C=O, amide	1682	1887

Source: Giordano et al. (1998).

8.2. ENANTIOTROPES AND MONOTROPES

There are two principal types of polymorphic pairs, one is a so-called monotropic pair. In this, one form is metastable relative to the other at all temperatures below the melting points of either. With enantiotropic pairs, however, there is a transition temperature, T_r , below which one form is more stable, and above which the other form is more stable. When there is more than two polymorphs, the situation may be a combination of these two situations.

The enantiotropic situation is best illustrated by a pressure–temperature (PT) diagram, such as shown in Fig. 8.1. Below the transition temperature T_r , form I has a lower vapor pressure. Transferring a mole of substance from point A to point B results in a decrease in energy (it is a voluntary process); hence, form II is unstable in relation to form I.

The situation is *not* referred to as instability, but rather as metastability, because if form II is kept cool and dry and, particularly, if it is not too finely subdivided, then it may stay as such for eons. Moisture, application of pressure, and comminuting will accelerate the change from II to I (from A to B). DSC traces in such cases often have the appearance of either (Fig. 8.2).

In the upper trace a sample of form I is heated slowly from room temperature up to its melting point. At $T_r = 25^\circ\text{C}$ there is an endotherm (caused by transition). Further heating of (the now) form II results in melting at $T_{II} = 101^\circ\text{C}$, the melting point of form II.

If heating is carried out rapidly, it is possible to “pass through” the transition temperature. This is shown in the lower curve in Fig. 8.2. At 72°C there will be an endotherm, owing to the melting of form I (i.e., $T_I = 72^\circ\text{C}$). However, there is now a thermodynamically unstable melt, and recrystallization is prone to occur. This is shown as the exotherm, occurring just above 72°C . This now forms solid form II, which on further heating, melts at 101°C .

Occasionally, the exotherm is missing, and when this occurs the melting endotherm of form II is also missing (i.e., the trace simply looks like the trace of melting form I, as if no other form existed (similar to the bottom trace in Fig. 8.4). In such a case, if the compound is stable, it may be recooled, and the down direction melting point can be (and most often is) that of form II.

In stable-cooling cycles, the heat events are exotherms, which are of the same magnitude, but of opposite sign, as the endotherms on the up-curve.

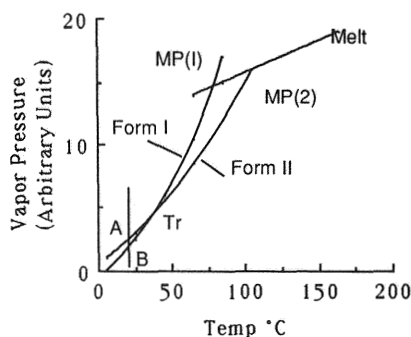


Fig. 8.1 Vapor pressure diagram of an enantiotropic pair.

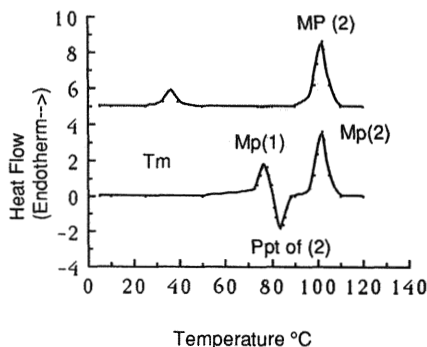


Fig. 8.2 Possible DSC traces resulting from heating of the room temperature-stable form of an enantiotropic pair.

The other case is monotropism (i.e., the situation where one form (form II) is metastable throughout the melting range). This is exemplified in Fig. 8.3.

The DSC trace of such a pair may take one of several forms. The stable form will simply show up as a trace with one endotherm (the melting point of the stable form). Traces of the metastable form may either show up this way, or they may show up as the middle trace in Fig. 8.4.

If the compound is stable to melting, it is advisable to recool the mass and record the melting point on the down trace. Most often, however, decomposition of the solid and melt preclude conclusions from cooling curves.

It follows from thermodynamics that the change in Gibbs' energy by a path from metastable to stable form ΔG , is given by

$$\Delta G = -RT \ln[P_{\text{metastable}}/P_{\text{stable}}] \quad (8.1)$$

In the top trace, it is the stable polymorph in Fig. 8.4 that is heated, and the two lower traces are the heating of the metastable polymorph, which may either simply melt (lower trace) or, as shown in the middle trace: melt, precipitate (exotherm) as the stable form I, and then (second endotherm) remelt.

It is negative, so the form with the highest vapor pressure at a given temperature is the least stable (metastable) compound.

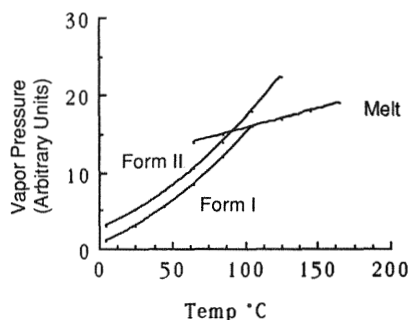


Fig. 8.3 Graph of vapor pressures for a monotropic pair.

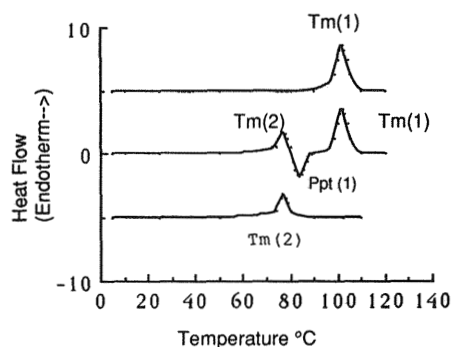


Fig. 8.4 Some possible DSC traces of the heating of polymorphs that are monotropic.

8.3. STABILITY OF METASTABLE POLYMORPHS: THE “DISAPPEARING” POLYMORPHS

Ostwald (1899) formulated a rule of stages: when a system first starts crystallizing, it initially will create the crystal structure that forms the smallest loss of free energy, and these crystals will later transform, stagewise, to the most (or a more) stable crystal structure.

There are several types of mechanism that can occur when a metastable, dry, polymorph transforms to a less energetic crystal form. If α denotes the amount transformed at time t , then some of the possibilities are elaborated in the following.

If the nucleation event is such that it can occur throughout the solid then there are three cases:

1. There are no complicating factors, the probability is time-independent, and the rate of transformation is given by

$$d\alpha/dt = k \quad (8.2)$$

where α is fraction converted, so that α simply increases linearly with time. This is the Polanyi–Winger equation:

$$\alpha = kt \quad (8.3)$$

2. The rate of transformation is directly proportional to the amount of solid not yet nucleated (frequently denoted “random nucleation”):

$$d\alpha/dt = k(1 - \alpha) \quad (8.4)$$

which integrates to

$$-\ln[1 - \alpha] = kt \quad (8.5)$$

3. The nucleation rate may also be proportional with time (i.e., the longer the elapsed time, the more likely is it that a site will transform).

$$d\alpha/dt = k^*(1 - \alpha)t \quad (8.6)$$

If, as an input function, the term

$$k^* = 2k^2 \quad (8.7)$$

is introduced, then

$$-d \ln[1 - \alpha] = 2k^2 t \quad (8.8)$$

which integrates to

$$-\ln[(1 - \alpha)] = k^2 t^2 \quad (8.9)$$

This is a form of the Avrami–Erofeev equation. An example of this is shown in Fig. 8.5.

4. Similarly, if the nucleation rate is proportional to t , but the nucleation can take place in three directions, then

$$-\ln[(1 - \alpha)] = k^3 t^3 \quad (8.10)$$

This, also, is a form of Avrami–Erofeev equation.

If, in two dimensions (exemplified by a cylinder transforming in a radial direction only; Fig. 8.6), the nucleation starts at the surface and works its way in, then the fraction not decomposed is given by

$$(1 - \alpha) = \pi(R - q)^2 / \pi R^2 = \pi(R - kt)^2 / \pi R^2 = [1 - (k/R)t]^2 \quad (8.11)$$

where q is the thickness of the transformed layer, and R is the radius of the cylinder. This may now be written:

$$[1 - (1 - \alpha)^{1/2}] = (k/R^2)t \quad (8.12)$$

Note that the rate constant (k/R^2) is larger, the smaller the particle (R).

It is easily shown that in three-dimensional diffusion, this becomes

$$[1 - (1 - \alpha)^{1/3}] = (k/R^3)t \quad (8.13)$$

again giving the same type dependence of particle size as in the cylinder example.

Examples of work in the pharmaceutical area are the publications of Umeda et al. (1985a,b) dealing with transformation of acetazolamide polymorphs and the work by Kaneniwa et al. (1985). Transformations are followed by disappearance (or appearance) of X-ray peaks, and the data are then plotted by the various equations, and the best-fit is found. In general, this is not a particularly good method (the data may plot well by many different equations), but in transformation rates, it works quite well.

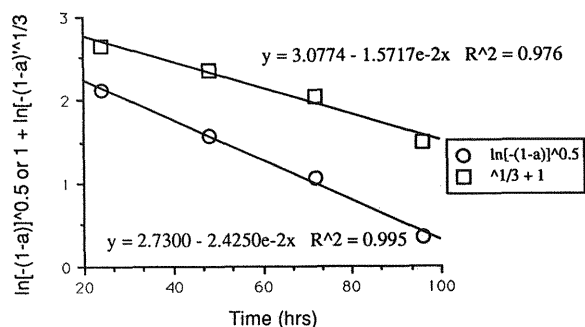


Fig. 8.5 Graph dealing with the conversion of (a) pure α -form and (b) crystals containing 1% of the γ -form. Adherence to Eq. (8.9) is better than that to Eq. (8.10). (Data from Kaneniwa et al., 1985.)

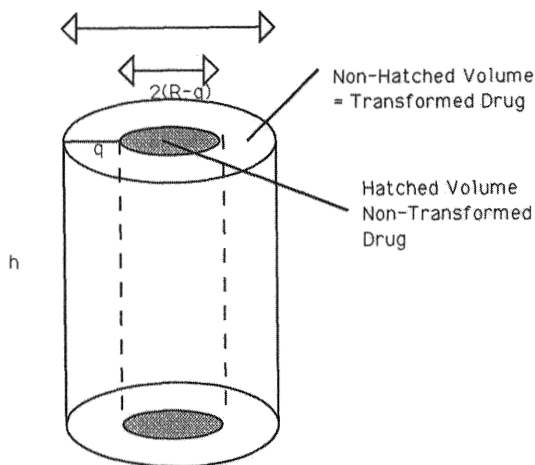


Fig. 8.6 Schematic of cylindrical model for linear decomposition.

Blagden et al. (1998a) reported on four different polymorphs of sulfathiazole. They (1998b) reported that an impurity in sulfathiazole synthesis, ethamidosulfathiazole, in concentrations as small as 1 mol%, stabilizes two of the metastable forms, form II and III, of the drug.

Attempts to find ways of stabilizing metastable polymorphs is of great industrial importance (Byrn et al., 1996), because the metastable polymorph may give better dissolution and bioavailability. Often impurities will induce twinning, which may inhibit the transformation, as with terephthalic acid (Davey et al., 1994). Sometimes additives may be used (e.g., polymers to prevent the change of the centric form of 3-*N*-ethamido-4-*N*-pyrrolidino nitrobenzene into the noncentric form) (Davey et al., 1997).

If the “initial” form of a new drug is a monotrope, and the stable form is unknown, then at one point in the development, seeds of the stable form may occur, and after this point it may be impossible to produce the metastable monotrope (Dunitz and Bernstein, 1995). I have had personal experience with such “disappearing” polymorphs in that, in the early 1960s, a batch of benzodiazepam was made that had a slightly (1°C) higher melting point than usual. The conventional wisdom was that the new batch was purer (for it had a lower melting point), but the truth was that it was a different polymorph, and after that batch had been made, it was impossible to recreate the “old” form. This, in turn, led to a large amount of duplication of clinical work, because the clinical results, up until that time, had been based on a metastable (more soluble), now unavailable polymorph.

8.4. RATES OF CONVERSION IN MOIST STORAGE

It can be shown by Henry's law that solubilities are (approximately) linearly related to vapor pressures (actually activities such as solubility are linearly related to fugacities). The graphs in Figs. 8.1 and 8.3 then become as shown in Figs. 8.7 and 8.8.

If the Henry's law argument is applied to Eq. (8.1), then

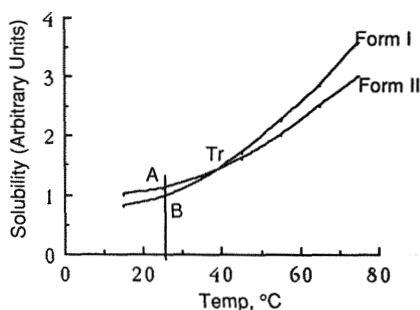


Fig. 8.7 Solubilities (in mass of solute per mass of solvent) of an enantiotropic pair.

$$\Delta G = -RT \ln[S_{\text{metastable}}/S_{\text{stable}}] \quad (8.14)$$

where S denotes solubility, R the gas constant, and T absolute temperature.

There are examples for which the solubilities are close over the entire temperature range (Carstensen and Franchini, 1984a,b) and, in such cases, it may be difficult to separate the two polymorphs in the final purification (recrystallization or reprecipitation), and there are cases where companies have been forced to suggest specifications that stipulate a minimum and a maximum of one polymorph in relation to another.

Graphs, such as those in Figs. 8.7 and 8.8 are often presented in log-inverse form:

$$\ln[S] = (-\Delta H_s/R)(1000/T) + \beta \quad (8.15)$$

where S is solubility, ΔH_s is the heat of solution at saturation, R is the gas constant, T is absolute temperature, and β is a constant. It is recalled, however, that ΔH_s is not necessarily temperature-independent (see Chapter 2), and if this is not true, then the Grant equation (Pudipeddi, 1998; Jozwiakowski et al., 1996) applies.

$$\ln S = -A/T + B \ln[T] + \beta \quad (8.16)$$

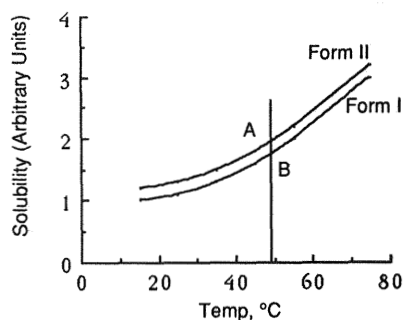


Fig. 8.8 Solubilities (in mass of solute per mass of solvent) of a monotropic pair.

8.5. MIXED POLYMORPHS

Reference is made to Figs. 8.7 and 8.8. The tendency of a metastable polymorph to convert to a more stable polymorph is a function of the difference in chemical energy. This, in turn [see Eq. (8.2)] is a function of their solubilities. If the curves in Figs. 8.7 and 8.8 are very close to one another (Carstensen and Franchini, 1994a,b), in particular, if the compound is very soluble, then the rate of transformation can be exceedingly slow, and the possibility of compounds crystallizing out in the two different crystal forms exists.

The regulatory authorities, presumably, are interested in the morphic purity of compounds because of the effect of polymorphism on bioavailability, and this, in turn, is tied to the solubility of polymorphs. The metastable forms have higher apparent solubilities than the stable forms; hence, they are likely to have higher bioavailabilities. However, in a situation as just described, the solubilities can be sufficiently close that one form is as bioavailable as another, under similar conditions (particle size, moisture content).

8.6. PSEUDOPOLYMORPHISM

One aspect of polymorphism is that the metastable form will have a higher “solubility” than the stable form. The word *solubility* has been placed in quotation marks, because theoretically a compound can only have one solubility. It has been seen, in Chapter 6, crystallization, that real equilibrium solubility happens only at infinite size of the particles, or at a secondary energy minimum. The point is that when the solubility is determined, an excess of solid is placed in contact with liquid that is stirred until “equilibrium” occurs. The facet of this solubility is that it is repeatable, so that for a metastable compound a reproducible number is arrived at, and this number is higher than the solubility of the more stable polymorph.

The molecules in solution, however, are the same, and the saturated solution of the metastable polymer is simply a supersaturated solution of the compound. Seeding it or waiting for a sufficiently long time will result in precipitation of the more stable polymorph.

One facet of polymorphism is, therefore, that solutions made from different polymorphs contain the same compound. If a hydrate is dissolved in water, then the solution will contain the same molecules as a solution made from the anhydrous material. For this reason, hydrates are called *pseudopolymorphs*. The prefix is derived from the fact that the *solid* composition differs (by water of crystallization). The same argument holds for a solvate and solutions in the solvent in question.

Mazuel (1991) and Golic et al. (1992) showed that norfloxacin forms different hydrates, and Sustar et al. (1993) showed that it forms at least two different crystalline forms. Mazuel (1991) and Golic et al. (1992) elucidated the crystal structure of norfloxacin, and Turel (1997) that of ciprofloxacin hydrates. The water is present in a complicated structure of hydrogen bonding. The manner in which the hydrate was made is as follows: The ciprofloxacin was dissolved in a 1:1 molar ratio of Cs_2CO_3 in water, and an addition of a few drops of 2 M sodium hydroxide would then clear up the solution. The crystals would grow in a couple of days (hexahydrate). When ammonia is used to dissolve the ciprofloxacin, then, depending on the ammonia concentration, either a tetra- or a hexahydrate is formed.

8.7. SOLUBILITY AND THERMODYNAMIC FUNCTIONS

There are often several (e.g., three different) polymorphic forms of an anhydrate, as well as solvates (Schnitzer et al., 1997) (e.g., there are three anhydrous, crystalline modifications of premafloxacin [forms I to III] and two solvates [a hydrate and a methanolate]). The DSC trace of form I is shown in Fig. 8.9. Note, that the upward peaks in this presentation are exotherms and that the events at approximately 145° and 170°C are endothermic conversions, with a subsequent exotherm (indicating a change in morphism to a more stable form), and that the lone endotherm at about 205°C implies a single endothermic change (e.g., melting) to a (physically) stable state (e.g., melt).

They determined the enthalpy of solution of each form and found values of -33.2 kJ/mol for form I and -24.4 kJ/mol for form III. The difference is 8.8 kJ/mol, form III having the lower enthalpy solid phase. They take this difference to be the difference in molar entropy of the two forms:

$$\Delta H_{I \rightarrow III} = -8.8 \text{ kJ/mol} \quad (8.17)$$

The solubilities in ethyl acetate were $s_I = 3.23$ mg/mL for form I, and $s_{III} = 0.14$ mg/mL for form III. They then employed the (approximate) Gibbs' relation.

$$\Delta G_{I \rightarrow III} = -RT \ln[s_I/s_{III}] \quad (8.18)$$

to calculate that

$$\Delta G_{I \rightarrow III} = -7.6 \text{ kJ/mol} \quad (8.19)$$

By employing the relation

$$\Delta G_{I \rightarrow III} = \Delta H_{I \rightarrow III} - T \Delta S_{I \rightarrow III} \quad (8.20)$$

and noting that both ΔH and ΔG were determined at $T = 298$ K it follows that

$$\Delta S = [-7.6 - (-8.8)]/298 = 0.004 \text{ kJ/mol} = 4 \text{ J/mol} \quad (8.21)$$

It follows, therefore, that the entropy term is rather insignificant in comparison with the enthalpy difference, and the authors conclude that *forms I and III constitute a*

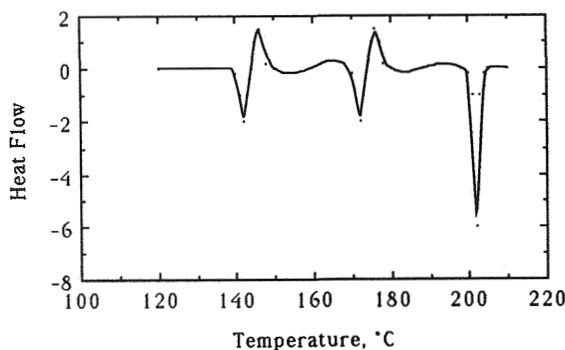


Fig. 8.9 DSC trace of form I of premafloxacin. Cooling and reheating produces only the endotherm at about 200°C. (Data from Schinzer et al., 1997.)

monotropic pair (i.e., the free energy of form III is lower than that of form I at all temperatures below the melting point).

There are two dangers in the approach taken by these authors (and many others, for that matter). The first is that Eq. (8.17) is based on bulk calorimetry; therefore, H is the integral heat of solution. To apply to saturated solutions, the enthalpy term should be the differential heat of solution at saturation (or near-saturation) conditions (Pudipeddi, 1996). The other is that Eq. (8.18) is correct *if activities, not concentrations, are employed*. It is true that in dilute solutions activity coefficients are close to unity, but they need not be so in concentrated solutions, and the important question is the magnitude of the ratio of activity coefficients at S_{III} and S_I . If one were, for example, 0.8 and the other 1.2, it would not seem to be all that serious, but the ratio would be off by 33% (or 50% whichever way one looks at it).

Because S is calculated from the difference of two numbers that are suspect, it is always dangerous to draw conclusions from its magnitude, in particular, if it is small.

There is an abundance of reports on polymorphs in today's pharmaceutical literature. For instance, Giordano et al. (1998) have reported on two polymers of piroxicam pivalate (PIRP). Polymorph I had the higher-melting point (153.8°) and polymorph II the lower (136.5°). Their fusion enthalpies were found by DSC to be 78.8 and 81.4 J/g. The "heat of fusion rule" (Giordano et al., 1998; Yu, 1995) states that if $\Delta H_{II} - \Delta H_I$ is positive, then enantiotropy is what is expected.

Kakkar et al. (1997) have prepared three crystalline forms of ciprofloxacin HCl, form I by cool evaporation from water, form II from cool evaporation from 1:2 water/methanol, both with a crystallization time of 50 h, and form III by cool evaporation from dimethylformamide. They furthermore prepared the amorphous form by lyophilization and by spray-drying. Some of the properties are shown in Table 8.3.

Some trends are noteworthy, and often apply.

The physically least stable is the amorphous and the most stable is form III, judging from the solubilities. The least stable crystalline form has the lowest density.

8.8. MIXTURES OF POLYMORPHS

Mixtures of polymorphs may occur, but the extent to which this may occur can be of great importance and cause great difficulty in product development. As an example,

Table 8.3 Ciprofloxacin-HCl Forms

Sample	Density (g/cm ³)	Melting point (°C)	No. of solvent moles per mole of drug	Solubility at 37°C (mg/cm ³)
Amorphous		316.7 ^a		70
Form I	0.796	313.5	3	54
Form II	0.980	312	1.5	45
Form III	1.042	316.3	0.5	34

^aSoftening point.

Bergren et al. (1996) have described two forms of delaviridine mesylate (forms VIII and form XI) both of which are anhydrous and nonhygroscopic.

Sarver et al. (1998), however, crystallized delaviridine mesylate from acetonitrile at room temperature as forms I and II. Both forms were very hygroscopic, and they subsequently recrystallized the compound from methanol under reflux. Acetone was added as a cosolvent. This produced either form XI or form VIII, depending on the amount of cosolvent used.

In distinguishing between the many polymorphs, Sarver et al. employed factor analysis (Malinowski and Howery, 1981), in which large sets of data can be segmented into smaller sets of orthogonal components. Of these, the first describes the largest variation in the data, and following components deal with variance of less and less variation. By this means it is possible to distinguish between polymorphs in mixtures.

8.9. DISSOLUTION RATES OF POLYMORPHS AND PSEUDOPOLYMORPHS

It has been shown in the previous sections that the less physically stable the polymorph or solvate, the higher is the solubility. Because dissolution rate, that is, the characteristic that is of importance biopharmaceutically, is directly related to solubility, there must be a connection between the two.

This has, indeed, been shown for phenylbutazone (Matsunga et al., 1976; Ibrahim et al., 1977; Müller, 1980; Tuladhar et al., 1983; Matsumote et al., 1988; Kaneniwa, 1988); for mefenamic acid (Aguir and Zelmeer, 1969); for diflunisal (Martinez-Oháriz et al., 1994); for indomethacin (Kaneniwa et al., 1985); for tenoxicam (Nabulsi et al., 1992); and for oxyphenbutazone (Stoltz et al., 1988).

Tros de Ilarduya et al. (1997) have described the dissolution behavior of pseudopolymorphs of sulindac. Table 8.4 shows the effect of solvates on dissolution rates.

It would appear from the data in the table that the solvates are metastable in relation to the non-solvate forms.

Crystal habit may affect dissolution rates as well (Carstensen, 1973; Burt and Mitchel, 1980, 1981; Chow and Grant, 1989).

The dissolution pattern of a metastable polymorph can be one of two types as shown in Fig. 8.10. The metastable solution may be fairly stable, so that the con-

Table 8.4 Dissolution Rates of Polymorphic Forms of Sulindac

Form	k (mg/min cm ³)
I	0.036
II (tabular habit)	0.031
II (hexagonal habit)	0.036
Acetate	0.076
Chloroformate	0.076

Source: Tros de Ilarduya et al. (1997).

centrations with time will approach the metastable solubility (the middle curve); at one point in time, the stable modification may start precipitating out, and the concentrations will drop and eventually approach that of the stable modification.

The latter phase is one manner in which *recrystallization* can be carried out strictly isothermally. The latter points of the precipitation in Fig. 8.10 (the middle curve) are frequently plotted semilogarithmically versus time.

8.10. RATES OF CONVERSION IN MOIST STORAGE

Good stability of a metastable compound can be achieved by (a) low temperature, (b) coarse crystals, and (c) dry storage. The moisture is the most serious contributor to conversion.

Moisture will condense onto the surface of the metastable form (II), and will then saturate the moisture layer to form a solution that is supersaturated in (I). This will eventually nucleate, and all of the II will convert to I.

The conversion rate, therefore, is a function of the nucleation rate in "solution," and it is a well known fact (Mullin, 1961), that the nucleation rate J is inversely proportional to the viscosity of the solution, and also to the supersaturation ratio ΔS , by the following relation:

$$J = A \exp\{q/[(T^3 \ln \Delta S) + (\Delta G_m/RT)]\} \quad (8.22)$$

an equation discussed in Chapter 7. For very soluble compounds, ΔS will be a very small number, and the tendency for one polymorph to change into another will be very small. Furthermore, if the solubility is high, then the ΔG_m terms will not differ much. An example of this is ranitidine (Carstensen and Franchini, 1994a,b).

SYMBOLS

ΔH_s = heat of solution at saturation, kCal/mole

R = gas constant

S = solubility, weight per weight of solvent

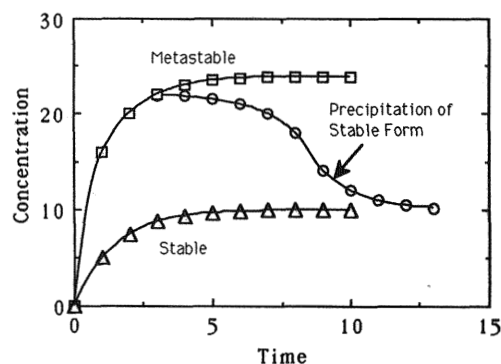


Fig. 8.10 Dissolution of (squares) a metastable polymorph; (circles) a metastable polymorph that on dissolution commences to convert to a stable modification, and (triangles) a stable polymorph.

T = absolute temperature

β = constant in the Van't Hoff equation

REFERENCES

- Aguiar AJ, Krc J Jr, Kinkel AW, Samyn C (1967). *J Pharm Sci* 56:847.
- Aguiar AJ, Zelmer JE (1969). *J Pharm Sci* 58:983.
- Burt HM, Mitchell AG (1980). *Int J Pharm* 5:251.
- Bergren MS, Chao RS, Meulman PA, Sarver RW, Lyster MA, Havens JL, Hawley M (1996). *J Pharm Sci* 85:834.
- Blagden N, Davey RJ, Lieberman H, Williams L, Payne R, Roberts R, Rowe R, Cochrerty R (1998a). *J Chem Soc Faraday Trans* 94:1035.
- Blagden N, Davey RJ, Rowe R, Roberts R (1998b). *Int J Pharm* 172:169.
- Burt HM, Mitchell AG (1981). *Int J Pharm* 9:137.
- Byrn SR, Pfeiffer RR, Stephenson G, Grant DJW, Gleason WB (1996). *Chem Mater* 6:1148.
- Carstensen JT (1973). *Theory of Pharmaceutical Systems*. Academic Press, New York, pp 145-147.
- Carstensen JT, Franchini M (1994a). *Pharm Res* 11S:267.
- Carstensen JT, Franchini M (1994b). *Drug Dev Ind Pharm* 21:523.
- Chow AH, Grant DJW (1988). *Int J Pharm* 51:115.
- Chow AH, Grant DJW (1989). *Int J Pharm* 51:123.
- Davey RJ, Magin, SJ, Andrews SJ, Black SN, Bucklely M.
- Dempsey P, Plowman R, Rout JE, Stanley DR, Taylor A (1994). *J Chem Soc Faraday Trans* 90:1003.
- Davey RJ, Blagden N, Potts GD, Docherty R (1997). *J Am Chem Soc* 119:1767.
- Dunitz JD, Bernstein J (1995). *Acc Chem Res* 28:193.
- Giordano F, Gazzaniga A, Moyano JR, Ventura P, Zanol M, Pever T, Carima L (1998). *J Pharm Sci* 87:333.
- Ibrahim HG, Pisano F, Bruno A (1977). *J Pharm Sci* 66:669.
- Jozwiakowski MJ, Nguyen NT, Sisco JJ, Spankack CW (1996). *J Pharm Sci* 87:193.
- Kakkhar AP, Singh M, Mendiratta A (1997). *Drug Dev Ind Pharm* 23:1063.
- Kaneniwa N, Otsuka M, Hayashi T (1985). *Chem Pharm Bull* 33:3447.
- Kaneniwa N, Ichikawa J, Matsumoto T (1988). *Chem Pharm Bull* 36:1063.
- Martínez-Ohárriz MC, Martín C, Goni MM, Rodríguez-Espinosa C, Tros de Ilardua MC, Sanchez M (1994). *J Pharm Sci* 83:174.
- Matsuda Y, Kawaguchi S, Kobayashi H, Nishijo J (1980). *J Pharm Pharmacol* 32:579.
- Matsumoto T, Ichikawa J, Kaneniwa N, Otsuka M (1988). *Chem Pharm Bull* 36:1074.
- Matsunaga J, Nambu N, Nagai T (1976). *Chem Pharm Bull* 24:1169.
- Mazuel C (1991). In: Florey K, ed. *Analytical Profiles of Drug Substances*. Academic Press, San Diego.
- Müller WW (1978). *Pharm Acta Helv* 53:333.
- Nabulsi L, Owais L, Arafat TA, Al-Kaysi H, Sheikh Salem M, Badwan AA (1992). *Bull Fac Pharm Jordan*, p 203.
- Ostwald W (1899). *Z Phys Chem (Leipzig)* 5:155.
- Pudipeddi M (1996). PhD dissertation, School of Pharmacy, University of Wisconsin, Madison, WI, p 86.
- Sarver RW, Meulman PA, Bowerman DK, Havens JL (1998). *Int J Pharm* 167:1105.
- Schinner WC, Bergren MS, Alddrich RS, Chao RS, Dunn MJ, Jeganathan A, Madden L (1997). *J Pharm Sci* 86:1426.
- Staab A, Addadi L, Leiserowitz L, Lahav M (1990). *Adv Mater* 2:40.
- Stoltz M, Lotter AP, Van Der Watt JG (1988). *J Pharm Sci* 77:1047.

Sustar B, Bukovec N, Bukovec P (1993). *J Herm Anal* 40:475.

Tros de Ilarduya MC, Martin C, Goni MM, Martinez-Uharriz MC (1997). *Drug Dev Ind Pharm* 23:1095.

Tuladar MD, Carless JE, Summers MP (1983). *J Pharm Pharmacol* 35:208.

deVilliers MM, Wurster DE, van der Watt JG, Ketkar A (1998). *Int J Pharm* 163:219.

Yu L (1995). *J Pharm Sci* 84:966.

This Page Intentionally Left Blank

9

Moisture Isotherms with Crystalline Solids

9.1. Substances that Are “Completely” Water-Insoluble	134
9.2. Moisture Adsorption or Absorption on or into Large, Crystalline Molecules	138
9.3. Crystalline, Non-hydrate-Forming, Water-Soluble Substances	138
9.4. Condensation Kinetics	140
9.5. Critical Moisture Content	142
9.6. Equilibrium Moisture Curves for Salt Hydrates	144
9.7. Presentation Mode of Water Vapor Pressure Versus Composition Diagrams	145
9.8. Equilibria of Compounds Forming a Crystalline Anhydrate and Only One Hydrate	146
9.9. Critical Temperature and Pressure	148
9.10. Equilibria of Compounds Forming a Crystalline Anhydrate and Two Hydrate Forms	150
9.11. Equilibria of Compounds Forming a Crystalline Anhydrate and More than Two Hydrate Forms	151
9.12. Moisture Equilibrium Curves of a Smooth Nature	153
9.13. Solvates	156
Symbols	156
References	157

When a solid is placed in an atmosphere, it will adsorb (or absorb, depending on the substance) moisture from the atmosphere. The *rate and extent* to which this occurs is usually referred to as *hygroscopicity*. As well as a kinetic property it also contains a thermodynamic one, and definitions, such as those used for solubility (e.g., very slightly and slightly soluble) are not possible. At best one may talk about very hygroscopic substance (choline salts, for instance) and very nonhygroscopic substances (sand, for instance), but the large gamut of substances call for more detail to describe their hygroscopic classification.

By its nature, the concept involves pickup of moisture, and that such pickup may be moderate at certain relative humidities and extensive at others indicates that classifications such as those used for solubility are not possible.

There are seven distinct categories of solids, which will be treated in separate section in the following:

1. Substances that are “completely” water-insoluble (e.g., silica)
2. Substances that do not form stoichiometric hydrates, but can *absorb* moisture by penetration (e.g., montmorillonite or cornstarch)
3. Crystalline substances that are (moderately or very) water-soluble, but do not form hydrates
4. Amorphous substances
5. Crystalline (anhydrous) substances that form one hydrate
6. Amorphous anhydrates that form one crystalline hydrate
7. Crystalline anhydrates that form several crystalline hydrates

9.1. SUBSTANCES THAT ARE “COMPLETELY” WATER-INSOLUBLE

There is always some water solubility associated with a compound, however poorly soluble, and the characterization “completely water-insoluble” should be taken in this vein.

An example of this is silica gel. This substance, owing to its large surface area, is often used as a desiccant in packaging of moisture-sensitive drugs and drug products. When silica gel is exposed to an atmosphere of a given relative humidity (RH), then as shown in Fig. 9.1 and Table 9.1, the weight of the sample will first rise fairly rapidly (the kinetic phase) and the rate of this is referred to as the *moisture uptake rate* (MUR).

In Fig. 9.1 it is noted that there is an (approximately) linear rate at low time points and these are shown in Fig. 9.2, and are seen to be *fairly* linear in RH at fairly low RH-values. In Fig. 9.1, it is also noted that the curves eventually level off. The equilibrium level is a function of the relative humidity at which the experiment is carried out. Table 9.2 shows an example of these equilibrium values at various relative humidities. The levels are tabulated in the second column of Table 9.2. The equilibrium values are plotted as a function of relative humidity in Fig. 9.3.

It is customary in isotherm work to convert these adsorbed amounts to the volume that would have been occupied at 0°C and 1 atm, and this can easily be done; for example, for the first row in Table 9.2, the number of moles is $n = 35 \times 10^{-3} / 18 = 19.5 \times 10^{-4}$ mol. The volume of this at 0°C and 1 atm would be $V = nRT/P = 19.5 \times 10^{-4} \times 8.2 \times 273/1 = 43.7$ mL. These figures are shown in

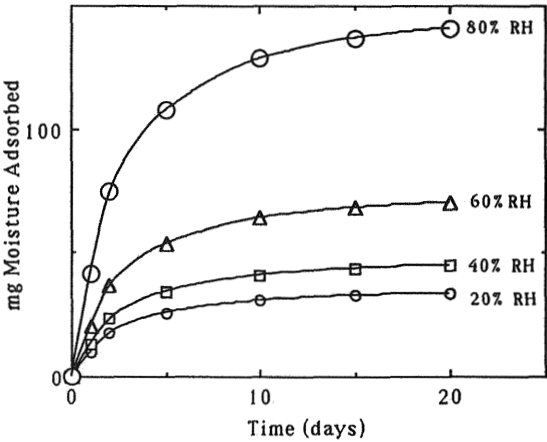


Fig. 9.1 Moisture uptake curves for a sample of silica gel at 20, 40, 60, and 80% RH.

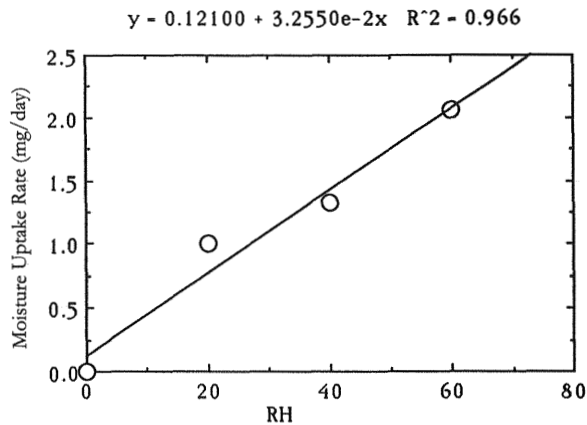


Fig. 9.2 Moisture uptake rates as a function of relative humidity for a “water-insoluble” compound.

Table 9.1 Typical Adsorption Data as a Function of Time

Time (days)	20% RH	40% RH	60% RH	80% RH
0	0	0	0	0
1	10	13.3	20.6	41.5
2	18	23.9	37.1	74.7
5	26	34.5	53.6	107.9
10	31	41.2	64.0	128.6
15	33	43.8	64.1	136.9
20	34	45.1	70.1	141.1

Table 9.2 Equilibrium Values and BET Parameters from the Data in Table 9.1

RH	Adsorbed (mg)	<i>V</i> (mL, STP)	RH/[<i>V</i> (100 – RH)]
0	0	0	
20	35.0	43.6	0.006
40	47.8	59.5	0.011
60	72.2	89.9	0.017
80	145.2	180.9	0.022

the third column and are denoted *V*. The *R*-value used is in units of cubic centimeters atmosphere (cm³atm).

As mentioned in Chapter 5, curves of this type are called BET isotherms [see Eqs. (5.57) and (5.58)]. The data in the third column are shown in Fig. 9.4. It can be shown that such data follow the BET equation:

$$RH/[V\{100 - RH\}] = (1/[V_m c] + \{(c - 1)/(cV_m)\}[RH/100])$$

(9.1)

Here, *V* is the volume (STP) adsorbed; *V_m* is the volume of a monolayer; *c* is the *c*-parameter in the BET equation, and the value of *c* is often large, so that the value of 1/[*V_mc*] may at times be neglected.

$$RH/[V\{100 - RH\}] = (1/V_m)[RH/100]$$

(9.2)

Treatment of the data in Table 9.2 by Eq. (9.1) is shown in Fig. 9.4.

V_m, as mentioned, is the adsorbed volume (0°C, 1 atm) of water that constitutes just one layer on the entire surface of the solid sample. RH/[*V*{100 – RH}] has been calculated in Table 9.2 (last column), and is plotted in Fig. 9.4 versus RH/100:

It is seen (as mentioned in Chapter 5) that

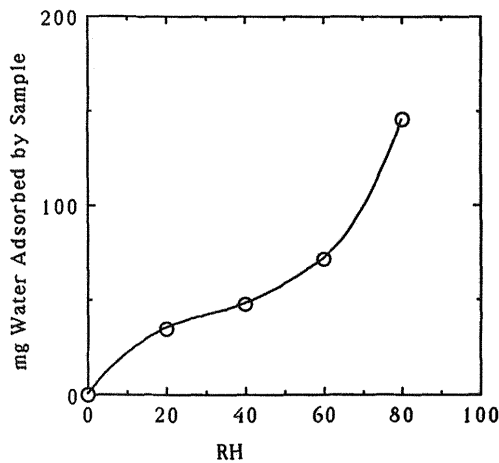


Fig. 9.3 Data from Table 9.2 plotted as adsorbed amount as a function of relative humidity.

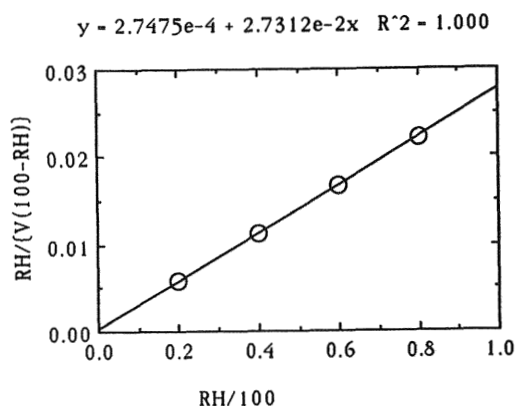


Fig. 9.4 Data in Table 9.2 treated by Eq. (9.3).

$$\text{Slope/intercept} = c - 1 \quad (9.2)$$

so that

$$c - 1 = 0.0273/2.75 \times 10^{-4} = 99 \quad (9.3)$$

so

$$c = 100 \quad (9.4)$$

Hence, we may use Eq. (9.2), such that

$$1/V_m = \text{slope} = 0.027 \quad (9.5)$$

that is,

$$V_m = 1/0.027 = 37 \text{ cm}^3 \quad (9.6)$$

This can be converted to moles (n) and then to molecules (N):

$$\begin{aligned} n_m &= PV_m/RT = 1 \times 37/[82 \times 273] = 16.5 \times 10^{-4} \text{ mol} \\ &= 6 \times 10^{23} \times 16.5 \times 10^{-4} = 10^{21} \text{ molecules} \end{aligned} \quad (9.7)$$

A cross-sectional area of $12.5 \times 10^{-20} \text{ m}^2/\text{molecule}$ of water is usually employed (Pudipeddi, 1996), so that in this example the entire surface area would be the number of molecules times the area of each molecule:

$$10^{21} \times (12.5 \times 10^{-20}) = 125 \text{ m}^2 \quad (9.8)$$

If the weight of the sample were 4 g, then the specific surface area would be $31.25 \text{ m}^2/\text{g}$.

If a bag of silica is placed in a bottle with a dosage form, then, if there is a critical moisture content beyond which the dosage form becomes unstable, it is possible to calculate from the isotherm of the dosage form, at which relative humidity this occurs. From the silica isotherm, one may then calculate how much moisture is taken up by the silica bag at this point, and dividing this figure by the moisture penetration of the package, it is possible to calculate the length of time the product is good. This will be covered further in the section under pharmaceutical packaging.

Moisture isotherms are of great significance in pharmaceuticals. Cases in points are the moisture isotherms of polyvinylpyrrolidone (PVP) and misoprostol-hydroxypropyl methylcellulose complex.

9.2. MOISTURE ADSORPTION OR ABSORPTION ON OR INTO LARGE, CRYSTALLINE MOLECULES

For an organic compound, such as starch, a smooth equilibrium moisture curve will result. Here again, there is the sharp upswing at very high relative humidities.

If experiments, such as exemplified in the foregoing are carried out on corn-starch, for example, then results of the *type* shown in Tables 9.1 and 9.2 and Fig. 9.3 result. When $RH/[V\{1 - P\}]$ is plotted versus RH , then a straight-line results.

Other examples include, for example, microcrystalline cellulose (MCC), which gives rise to BET isotherms. The surface area obtained from them is, however, manyfold larger than the area obtained by nitrogen adsorption. Marshall et al. (1972) and Zografi and Kontny (1986) have shown that water penetrates the solid, and that each OH group in the MCC constitutes an adsorption (absorption) site.

9.3. CRYSTALLINE, NON-HYDRATE-FORMING, WATER-SOLUBLE SUBSTANCES

Compounds of this nature are, for instance, organic, nonprotic compounds (e.g., sucrose), organic electrolytes (e.g., choline salts), and several electrolytes (e.g., sodium chloride).

This phenomenon has been dealt with by Van Campen et al. (1980). The purpose here is to derive a rational equation for the rate with which moisture is adsorbed onto a water-soluble solid.

As mentioned, if a solid is evacuated (Fig. 9.5a) and then placed in an atmosphere that has a vapor pressure P_a , which is *lower* than the vapor pressure P_s of the saturated solution of the compound, then (see Fig. 9.5a,b), moisture will adsorb onto its surface by the same process as nitrogen in a BET-experiment.

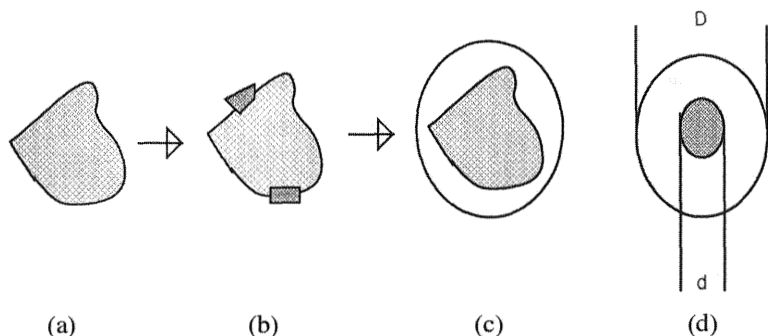


Fig. 9.5 Modes of moisture adsorption: (a) evacuated solid; (b) active sites (BET model applies, below the critical relative humidity); (c) bulk, saturated solution at exactly the critical relative humidity; (d) bulk, unsaturated solution at RH values above the critical relative humidity.

However (see Fig. 9.5c,d), once the vapor pressure in the atmosphere P_a equals that of the saturated solution of the compound P_s , then the condition exists in which a *bulk layer of moisture* is thermodynamically feasible.

If $P_a > P_s$ and the volume of the atmosphere is infinite, then water will condense onto the solid, and the solution formed will be saturated (because it is in equilibrium with a solid phase). This will continue until all the solid has dissolved, a phenomenon known as *deliquescence*. It will, however, *continue until the concentration of the now unsaturated solution is such that its vapor pressure matches that of the atmosphere* (i.e., until it is P_a), because nature will attempt to establish equilibrium. A consequence of this is that if a solid is placed in an atmosphere of 100% RH, then condensation will continue *ad infinitum*, if the volume of the vapor phase is infinite, because in this case nature will attempt to establish the equilibrium that exists at a concentration of solute of zero (pure water).

Because vapor-phase volumes of infinity are not within the realm of the possible, it is worthwhile to consider a more realistic situation for which these principles apply.

The following nomenclature will be used in the following:

V = volume of vapor phase

P_a = water vapor pressure of vapor phase before condensation

P_x = water vapor pressure of vapor phase after condensation

P_0 = water's vapor pressure at a temperature of T

R = ideal gas constant

T = absolute temperature

w' = moles of water condensed

s = solubility of compound in moles/mole of water

n = number of moles of solid dissolved

We now distinguish between two situations: (a) one where there is insufficient water present in the vapor phase to dissolve all the drug (and a so-called *bulk moisture layer* is formed), and (b) where there is sufficient moisture in the vapor pressure to dissolve all the drug and form an unsaturated solution (*deliquescence*).

With the cited nomenclature and the situation depicted in Fig. 9.6 it follows that, with insufficient moisture for deliquescence, the amount of moisture condensed is such that the amount of solid dissolved is given by $w's = n$.

$$w' = n/s \quad (9.9)$$

After condensation the vapor pressure will be P_s . This quantity is very significant because, when the subject is the stability of drugs in exposure to moist atmospheres, *this is the amount of the sorbed bulk moisture layer and this dictates the expected stability rate of the drug substance*.

In the case of deliquescence, the solution formed is not saturated, but will have a concentration of n/w' (i.e., the mole fraction in solution will be

$$x = \{n/w'\} / \{1 + (n/w')\} = n/(n + w') \quad (9.10)$$

If the solution is considered ideal, then the vapor pressure P_x , after equilibrium has set in, will be

$$P_x = P_0(1 - x) = P_0\{w'/(n + w')\} \quad (9.11)$$

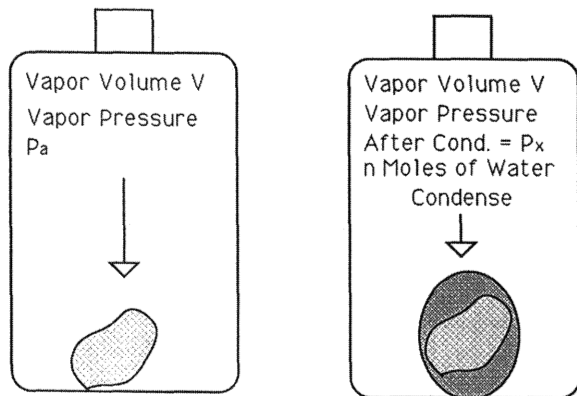


Fig. 9.6 Schematic for moisture adsorption on a solid in a closed container.

Here, n is known, as it is the number of moles of solid (all of which have dissolved). P_x is related to w' by the ideal gas relation

$$(P_a - P_x)V/RT = w' \quad (9.12)$$

Eqs. (9.11) and (9.12) constitute two equations with two unknowns (P_x and w'), and can be solved.

9.4. CONDENSATION KINETICS

In the following, it will be assumed that the foregoing situation (a) exists (i.e., that the condensed water will dissolve solid), and it will be assumed that the sorbed solution is saturated at all times. The question is, what sort of curve might be expected for the extent of moisture uptake with time (the moisture uptake rate curve; the MUR curve).

A further assumption is that the amount of moisture adsorbed does not, to a great extent, change the vapor pressure in the atmosphere surrounding the solid particles.

Assume that, at time t (Carstensen, 1986), a certain amount of moisture, w (grams) has been adsorbed by a particular solid particle weighing m grams and of diameter d_0 , at which the subscript denotes the condition before moisture adsorption. At time t , moisture will have adsorbed, some solid will have dissolved, and the diameter d of the solid itself will have decreased from its original value. The diameter of the ensemble D is the sum of the diameter of the remaining solid, and the thickness h of the moisture layer.

It is assumed in the following that 1 g of solid is studied and that the sample is monodisperse. Such a sample would consist of N particles where:

$$Nm = N\rho\pi d_0^3/6 = 1 \quad (9.13)$$

The amount of solid present at time t is given by the original amount less the amount dissolved. If there are W grams of water adsorbed by 1 g of solid (i.e., w grams dissolved per particle), then,

$$N(\rho\pi/6)d^3 = N(m - wS) = 1 - WS \quad (9.14)$$

where S is solubility in gram/gram. Therefore:

$$d^3 = (1 - WS)/(N(\rho\pi/6)) \quad (9.15)$$

The volume of liquid adsorbed by one solid particle has a volume of the total particle minus the solid particle; that is,

$$\begin{aligned} w/\rho^* &= (\pi/6)D^3 - (\pi/6)d^3 \\ &= (\pi/6)D^3 - \{(\pi/6)(1 - WS)/(N(\rho\pi/6))\} \end{aligned} \quad (9.16)$$

where ρ^* is the density of the adsorbed liquid. Because it is assumed that it is always saturated, it is time-independent, and under ideal conditions it would be

$$\rho^* = (1 - x_s)\rho_0 + x_s\rho \quad (9.17)$$

where $(1 - x_s)$ and x_s are the volume fractions of liquid and solid, respectively, in the ensemble particle, and ρ_0 and ρ are the respective densities. It follows from Eq. (9.17) that the amount of moisture adsorbed per gram can be expressed in terms of diameters as follows:

$$W = \rho^*N(\pi/6)D^3 - [\rho^*(1 - WS)/\rho] = QD^3 - F + FSW \quad (9.18)$$

where

$$F = \rho^*/\rho \quad (9.19)$$

$$Q = \rho^*N(\pi/6) \quad (9.20)$$

Equation (9.18) may be written:

$$F + (1 - FS)W = QD^3 \quad (9.21)$$

or

$$D = \{[F + (1 - FS)W]/Q\}^{1/3} \quad (9.22)$$

The area a of the particle (solid plus liquid) is, hence,

$$a = \pi\{[F + (1 - FS)W]/Q\}^{2/3} = B[E + W]^{2/3} \quad (9.23)$$

where

$$B = \pi\{[1 - FS]/Q\}^{2/3} \quad (9.24)$$

$$E = \{FQ/(1 - FS)\}^{2/3} \quad (9.25)$$

The rate of condensation (dW/dt) is proportional to the pressure gradient (i.e., the difference between the water vapor pressure P in the atmosphere and the vapor pressure P_s over a saturated solution). At a given atmospheric milieu, this gradient is a constant.

It is also proportional to the surface area a , by a mass transfer coefficient k , so that we may write:

$$dW/dt = ka(P_a - P_s) = k(P_a - P_s)B[E + W]^{2/3} \quad (9.26)$$

where Eq. (9.23) has been used for the last step. This may be written:

$$dW/[E + W]^{2/3} = 3Gdt \quad (9.27)$$

where

$$3G = k(P - P_s)B \quad (9.28)$$

Equation (9.27) integrates to

$$[E + W]^{1/3} = Gt + [E]^{2/3} \quad (9.29)$$

where the initial conditions that $W = 0$ at $t = 0$ has been imposed. Equation (9.29) can be solved by iteration.

As an example of this, VanCampen et al. (1980) studied the moisture pickup in a vacuum system by using a Cahn balance, and exposing the evacuated head space to relative humidities created by salt baths. They also reported moisture uptake rates of choline chloride at room temperature and different relative humidities using a desiccator method. An example of their results obtained by the latter method is shown in Fig. 9.7.

9.5. CRITICAL MOISTURE CONTENT

There are humidities below which a solid will not adsorb (considerable amounts) of moisture (i.e., will not form a “bulk-sorbed” layer). As already covered to some extent, these are dictated by the solubility of the compound. Jakobsen et al. (1997) have discussed this situation for three drug substances.

Suppose a solid with a high solubility is placed in a room of a given RH, as shown in Fig. 9.8. If the RH were 30%, then it might pick up moisture at a given rate, at 50% RH at a higher rate, and at 80% RH at an even higher rate.

The rate with which it picks up moisture is determined by weighing the sample at given intervals, as demonstrated in Table 9.3. It is noted that there is a linear section of the curve (up to 6 days) as shown in Fig. 9.9. The slope of this linear segment is the moisture uptake rate (MUR). The actual uptake rates (determined from the linear portions) are shown in Table 9.4.

The uptake rates can be simply obtained by weighing the sample after a given time (6 days), but in such a case it is assumed that the moisture uptake is still in the

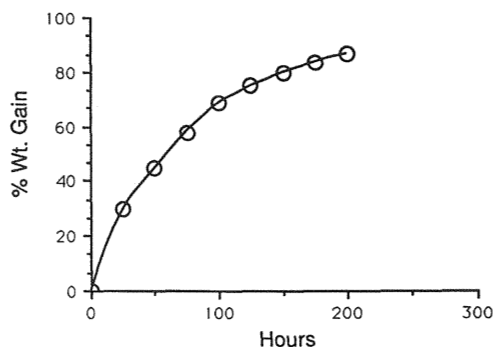


Fig. 9.7 Data for choline chloride moisture adsorption at 100% RH. (Data from VanCampen et al., 1980.)

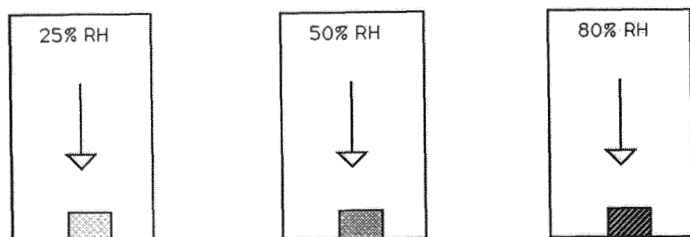


Fig. 9.8 Mechanism of moisture uptake.

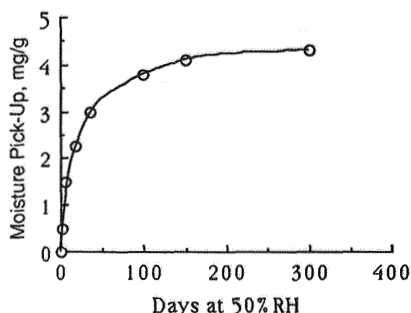


Fig. 9.9 Moisture uptake data from Table 9.3.

linear phase. If, for example, the weight gain is 5 mg/10 g sample in 6 days, then the MUR is $5/10/6 = 0.083$ mg/g/day.

If the MUR values are plotted versus RH, then a straight-line results (Fig. 9.10). It is noted that the curve, in this case, intercepts the x -axis at 20% RH. This means that the compound can be stored without moisture pickup in atmospheres of less than 20% RH. In some cases the compound will dry out under such conditions (e.g., a hydrate), but in general the useful information reached from such a graph is the maximum RH that is satisfactory for storage of the product; 20% RH happens to be the relative humidity over a saturated solution of the compound (or over a salt pair, as will be discussed presently).

Table 9.3 Moisture Uptake of a Highly Water-Soluble Compound at 50% RH

Days stored at 50% RH	Moisture pickup (mg/g)
2	0.5
6	1.5
18	2.25
36	3.4
100	3.0
144	4.2
288	4.3

Table 9.4 Moisture Uptake Rate of Water-Soluble Compound

% RH	mg/g/day
25	0.1
50	0.25
80	0.45

It is known as the *critical moisture content and the critical relative humidity*, for a non-hydrate-forming compound. Curves, such as the one shown in Fig. 9.10, for most salts intersect at much higher relative humidities. Because the value is related to the solubility of the compound, and this, on a mole fraction scale, is a rather small number, the saturated solution is often (nearly) ideal, and the reverse procedure may be used; namely, from plots such as that in Fig. 9.10 and the deduced value of the critical relative humidity RH^* , the mole fraction at saturation y may be calculated from

$$RH^* = 1 - y \quad (9.30)$$

9.6. EQUILIBRIUM MOISTURE CURVES FOR SALT HYDRATES

The previous section dealt with the *rate* with which moisture is taken up. As shown in Fig. 9.9, at longer time periods, the moisture level (the weight of the sample) will taper off and plateau at an equilibrium value. This equilibrium value is also a function of RH, and there are two types of curves that occur when equilibrium values are plotted against RH: salt pairs and continuous adsorption. The former will be discussed first.

Many compounds, especially ionic compounds, form hydrates. A *hydrate* is defined as a *chemical compound with a rational ratio of water to anhydrous compound at different temperatures*.

It is visualized that the water molecules occupy definitive positions in the crystal lattice. In some cases (e.g., montmorillonite), different amounts of water

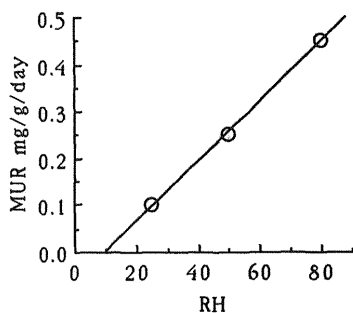


Fig. 9.10 Moisture uptake rate as a function of RH. Least-squares fit is $y = -0.06264 + 0.006374x$, with $R^2 = 0.999$.

may be adsorbed or absorbed, and the crystal spacings between the layers of aluminum magnesium silicates increase in proportion, but the curve is continuous (i.e., shows no inclination to be stepwise in nature). This is an intermediate case, and hydrates usually have stepwise profiles when equilibrium vapor pressure is plotted versus composition. The question is then whether this water sits "in a channel" (as apparently it does in montmorillonite) or is bound in a different manner. Occasionally, the water molecules are part of the coordination shell of an ion, as for instance in magnesium chloride, which exists as, among others, a dihydrate and a tetrahydrate. The anhydrate can be produced by interaction between metallic magnesium and hydrochloric acid gas. Heating magnesium chloride tetrahydrate to 80–100°C will remove two of the molecules of water. But further heating results in the removal of 2 mol of hydrochloric acid, leaving magnesium hydroxide behind.

The cases that will be discussed in the following are of the type for which an anhydrate can be produced by heating or by vacuum.

9.7. PRESENTATION MODE OF WATER VAPOR PRESSURE VERSUS COMPOSITION DIAGRAMS

The vapor pressure of a salt hydrate as a function of "composition" will be referred to in the following simply as the *vapor pressure profile of the hydrate*. Some of the concepts to be discussed are quite ancient, but since thermodynamics are not a function of the calendar time at which they were formulated, they are presented with reference to original works. There is a great deal of *reinvention* in the field, primarily because automated literature searches usually do not go farther back than 1970.

There are different conventions for presentation and the one proposed by Brønsted (1943) is as follows (Fig. 9.11).

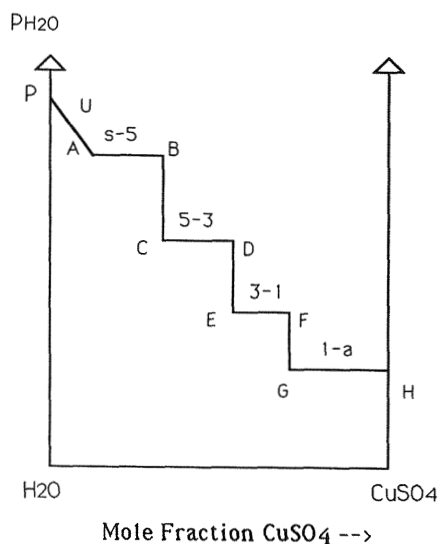
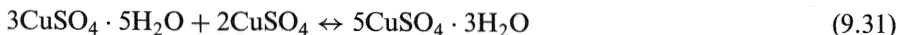


Fig. 9.11 Vapor pressure profile for CuSO_4 hydrates. (Data from Brønsted, 1943.)

Brønsted (1943), as opposed to convention nowadays, considers water the left ordinate axis, and starting at point P, pure water's vapor pressure, salt is added to form unsaturated solution (u). At point A the aqueous phase is saturated with copper sulfate, and the solid phase is the pentahydrate. If sufficient copper sulfate is added to point B, then the interchange in Eq. (9.31) occurs:



In this phase the two solid phases: trihydrate and pentahydrate, are in equilibrium. According to Gibbs' phase rule, at the given temperature, between the two extremes (see C and D in Fig. 9.11) (a) all pentahydrate and (b) all trihydrate, the water vapor pressure must stay constant. This is called a *salt pair*, and is characterized by the fact that the water vapor pressure stays constant as long as both salts are present (i.e., the water vapor pressure is independent of concentration of each during this interval).

Once enough copper sulfate has been added to the system to convert all of it to trihydrate, the next addition of copper sulfate will cause a new conversion (i.e., the conversion of trihydrate to monohydrate (see EF in Fig. 9.11), and once this is complete an equilibrium between monohydrate and anhydrate will establish itself.

The diagram is convenient at the endpoints, for instance. If the solution is ideal, then the curve PA will be a straight line, if not, then it will be curved.

In more recent literature, different plotting conventions have prevailed. In general the direction of the x -axis is reversed, so that the amount of water is increased from 0 to 1 mol fraction. But furthermore, present-day convention does not employ mole fraction, but rather grams of water per gram of solid. This complicates the ends of the diagram, because one cannot represent pure water in this fashion. Finally, most authors plot relative humidity on the x -axis and water content on the y -axis. For convenience, the discussion to follow *about salt pairs* will use the presentation mode for which water vapor pressure is plotted on the y -axis and *weight of water per weight of solid* is used on the x -axis.

In presentations on amorphates, the axes will be reversed as conventional with isotherms.

9.8. EQUILIBRIA OF COMPOUNDS FORMING A CRYSTALLINE ANHYDRATE AND ONLY ONE HYDRATE

In the situation depicted in the previous sections, the compound (copper sulfate) was capable of existing in a crystalline anhydrate and several hydrate forms. Frequently, only one hydrate form exists, such as lactose monohydrate and potassium tartrate dihydrate.

If an anhydrate can interact with moisture to give a hydrate, say an x -hydrate, then the reaction involved is



The equilibrium constant is given by

$$K = P_{\text{H}_2\text{O}}^x \quad (9.33)$$

The general situation is depicted in Fig. 9.12. This diagram applies to one particular temperature and when the water activity ($a = \text{RH}/100$) is low, only the anhydrate exists. At a given value of a , a_1 , however, the x -hydrate will start forming,

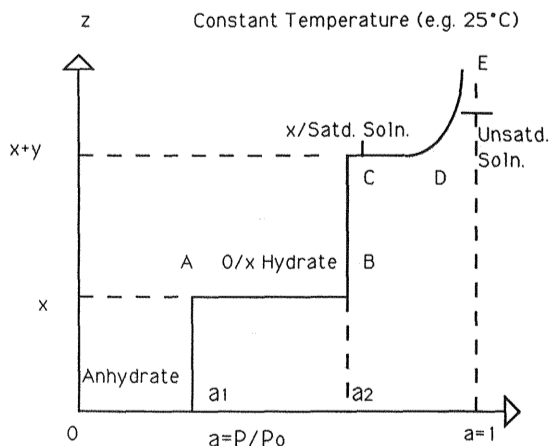


Fig. 9.12 $X - P$ diagram for a compound that forms (only) a monohydrate.

and with infinite volume vapor phase the reaction according to Eq. (9.32) will complete (line AB). Increasing the vapor pressure to between a_1 and a_2 will not change the hydrate (but will cause some surface adsorption). At a_2 , however, the vapor pressure is equal to the vapor pressure of a saturated solution, so water will start condensing, and (with an infinite vapor phase volume) adsorption will continue (line BC) until all the salt has *just* dissolved to create one phase.

If the vapor pressure is further increased, then dilute solutions will form and the profile, if the solutions are ideal, will be as shown in the CDE part of the curve.

From Eq. (9.33) it follows that

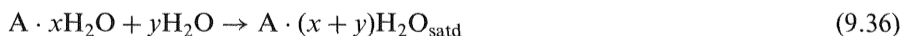
$$\partial \ln P / \partial T = \Delta H / xRT^2 \quad (9.34)$$

which, if ΔH is temperature-independent can be integrated to

$$\ln[P] = -\{\Delta H / xRT\}(1/T) + q \quad (9.35)$$

P is here water vapor pressure, ΔH is the enthalpy involved with one molecule of water, x is the number of moles of hydrate water per mole of compound, and q is a constant. It is seen in Fig. 9.13 (potassium tartrate dihydrate) that when ΔH is fairly temperature-independent, then log-inverse temperature plots are linear.

The slopes of the vapor pressure over the salt hydrate and the saturated solution differ because the enthalpy from the slope of the hydrate is for the reaction shown in Eq. (9.33), whereas the enthalpy for the saturated solution is for the reaction:



Vapor pressures over salt hydrate pairs also increase with temperature (Table 9.5).

The situation, hence, is that the vapor pressure of the x -hydrate will increase with temperature as will the vapor pressure of a saturated solution of the compound. In Fig. 9.13 neither the salt pair nor saturated solutions have a vapor pressure of 760 mmHg (1 atm) until a temperature of 115°C is reached.

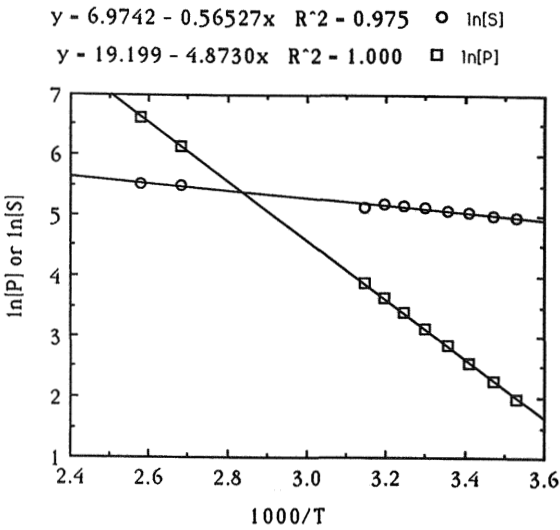


Fig. 9.13 Vapor pressure data and solubility data of $K_2C_4H_4O_6$. (Data from Krack, 1998.)

9.9. CRITICAL TEMPERATURE AND PRESSURE

In the situation shown in Fig. 9.13, the hydrate stays as such in the entire temperature range of 10–115°, and the general shape of the diagram in Fig. 9.12 would apply at any temperature in this region.

The vapor pressure of both salt hydrate and saturated solution increases with temperature, and (as seen in Fig. 9.13) when the solubility increases with temperature its vapor pressure most often increases more rapidly for the hydrate than for the saturated solution.

Therefore, there will often be the case (see Fig. 9.14) where the x-hydrate achieves the same vapor pressure as the saturated solution vapor pressure and temperature. This is denoted *the critical temperature* and at temperatures above this temperature only the anhydrate is thermodynamically stable.

For a monohydrate as depicted in Fig. 9.14, the increase in vapor pressure over the salt hydrate will increase drastically once more than 1 mol of water is present per

Table 9.5 Influence of Temperature on Vapor Pressure (mmHG) of Salt Pairs

Temperature (°C)	$NaHPO_4 \cdot 12H_2O \rightarrow NaHPO_4 \cdot 7H_2O + 5H_2O^a$	$SrCl_2 \cdot 6H_2O \rightarrow SrCl_2 \cdot 6H_2O + 4H_2O^b$
0	2.66	1.23
15	8.95	4.0
20	12.93	8.4
25	19.18	
30	27.05	

Source: ^aPartington and Winterton (1930); ^bBaxter and Lansing (1920).

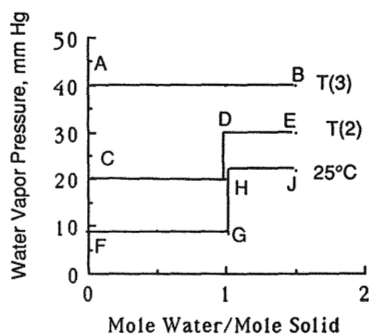


Fig. 9.14 Single salt pair (monohydrate) vapor pressures as a function of temperature. The line at point A has been drawn slightly to the left for graphic clarity. It occurs at 1 mol of water per mole of solid. (Data from Carstensen, 1986.)

mole of solid. Moisture will then keep on condensing and converting the monohydrate to saturated solution, and this will continue until all is dissolved. After that the vapor pressure will increase so that it is always in equilibrium with the concentration in the (now) unsaturated solution.

The diagram in Fig. 9.14 is at a given temperature and shows a compound capable of forming a monohydrate at different temperatures. At the temperature T_3 the line for the salt pair has “caught up” with that of the saturated solution. Above T_3 the salt would have a higher vapor pressure than the saturated solution, but this is thermodynamically untenable, and T_3 is simply the highest temperature (and a triple point) at which the monohydrate exists. It is the *critical* temperature for the hydrate.

If a saturated solution consisted of 1 mol of salt and y mol of water, then vapor pressure of the saturated solution, if it were ideal, would be

$$a = P/P_0 = y/(y + 1) \quad (9.37)$$

At higher relative humidities, water will condense on the solid to form an unsaturated solution. If this is ideal, then adding z mol of water to 1 mol of solid would give a mole fraction of

$$a = P/P_0 = 1 - [1/(z + 1)] = z/(z + 1) \quad (9.38)$$

so that

$$z = a/(1 - a) \quad (9.39)$$

as $a \rightarrow 1$; $z \rightarrow \infty$. The shape of this curve is as shown in the curve in the right hand section (CDE) of Fig. 9.12.

The data presentation in mole fraction (see Fig. 9.11) is simpler, because the section PA is simply a straight line, if the solution is ideal. It follows from Eq. (9.39) that at 100% RH the system in equilibrium is infinite dilution (pure water), and if a diagram as this is carried out to 100% RH, then a sharply increasing curve should result at very high RH.

9.10. EQUILIBRIA OF COMPOUNDS FORMING A CRYSTALLINE ANHYDRATE AND TWO HYDRATE FORMS

If there are two salt pairs, an m - n , an n -0 pair ($m > n$), there are two possible situations. One is that the m -form's critical temperature (K in case B in Fig. 9.15) is below that of the n -form's critical temperature (L in case B in Fig. 9.15). The other (hypothetical) case is where the m -form's critical temperature (N in case A in Fig. 9.15), is above the critical temperature M , of the n -form (case A in Fig. 9.15). In the latter, hypothetical case the m - n vapor pressure curve crosses that of the saturated solution (denoted s) at T^* , and above this temperature it would (if it existed) give rise to a situation in which the vapor pressure of the m -salt would be higher than that of the saturated solution. This is not feasible thermodynamically, so that the critical temperature for the m -hydrate in this case would have to be the point at which it reaches the vapor pressure of saturated solution. Such a case has been reported by Chen and Grant (1998) for nedocromil the sodium trihydrate/monohydrate system. Erroneously, Fig. 1 of that publication fails to show three plateaus, and the nick in the saturated solution vapor pressure curve(s) is absent.

The correct profile for this situation is depicted graphically as case B in Fig. 9.15, and schematically in Fig. 9.16. Noteworthy are the nicks in the solubility curve at temperatures T^* and N and at K and L .

Often, when there is a transition between two salt pairs there will be an intersection between m - n and n -0, and above the transition the stable species will be m -0 (Brønsted, 1943). A diagram similar to that of Fig. 9.14 is shown for cases A and B in Fig. 9.16.

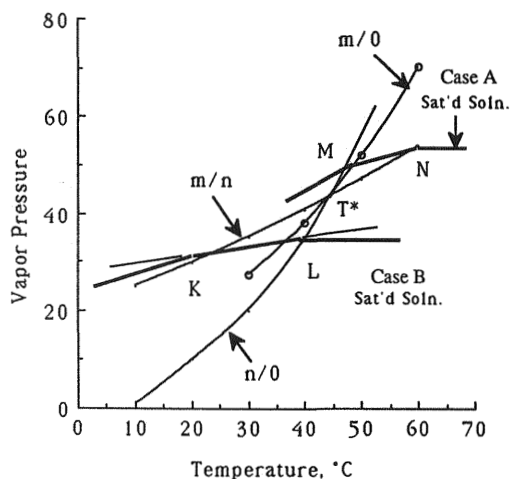


Fig. 9.15 Water vapor pressure diagrams of a compound forming two hydrates. In the first situation there is a conversion below the boiling point of water, in the second the mn -hydrate vapor pressure reaches the vapor pressure of the saturated solution above the boiling point of water. Note the nicks in the saturation curve at points K and L . Often (but not shown in the figure), if there is a transition between two salt pairs there will be an intersection between, for example, m - n and n -0, and above the transition the stable species will be m /0. (From Brønsted, 1943.)

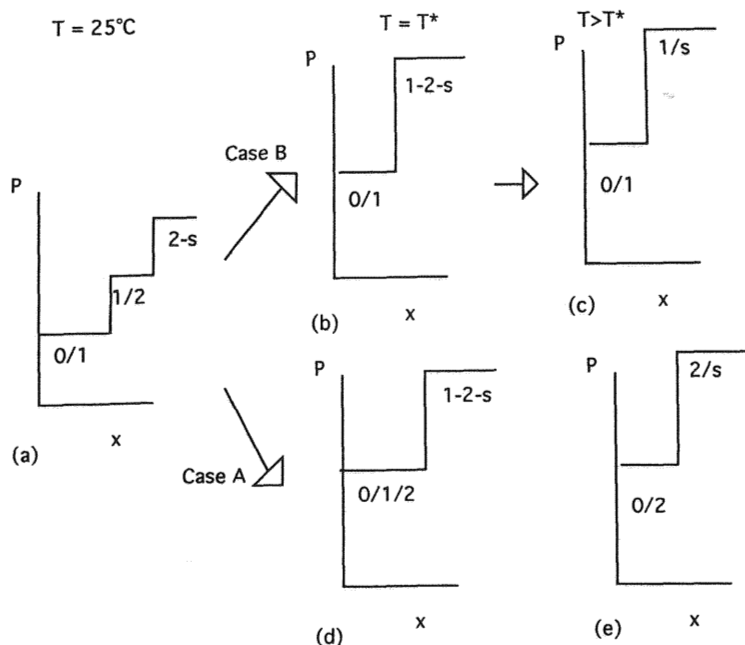


Fig. 9.16 There are two distinct situations hypothetically possible: (i) as temperature increases, the dihydrate vapor pressure would reach its critical point T^* , when its vapor pressure would equal that of the saturated solution (Fig. 9.16(b)). At $T > T^*$ the diagram would simply be a $P - x$ diagram of a single hydrate (the monohydrate, Fig. 9.16(c)). The solid phase in equilibrium with saturated solution would be the monohydrate. There would be a nick in the vapor pressure curve at T^* . (b) As temperature increases, the vapor pressure of the monohydrate will reach that of the dihydrate at a critical temperature, T^* , for the monohydrate (Fig. 9.16(d)). Above T^* , the monohydrate, if it existed, would have a vapor pressure above that of the dihydrate, which is not possible, so at $T > T^*$ the $P - x$ diagram will be that typical of a single hydrate (i.e., the dihydrate, Fig. 9.16(e)). It is noted that there is a nick in the vapor pressure curve.

9.11. EQUILIBRIA OF COMPOUNDS FORMING A CRYSTALLINE ANHYDRATE AND MORE THAN TWO HYDRATE FORMS

An example of this situation has already been described, albeit it not in detail, in Fig. 9.11. The numerical data (Na_2HPO_4), are shown in Table 9.6. The compound can form three hydrates (2, 7, and 12) aside from a crystalline anhydrate. In the usual presentation mode (i.e., not using molar concentration and content units), the percentage of moisture in the dihydrate, for example, is calculated as follows: disodium hydrogen phosphate has a molecular weight of 142; hence, the dihydrate has a molecular weight of $142 + 36 = 178$; accordingly, the moisture percentage is $100 \times (36/178) = 20\%$. The moisture contents for the remaining hydrates are shown in Table 9.6. It is seen in the table (and from Fig. 9.17) that the relative humidity of the atmosphere above a mixture of anhydrous disodium hydrogen phosphate and the dihydrate is 9 mmHg or $100 \times (9/24) = 38\%$ RH. Any mixture of the anhydrous salt and the dihydrate will give this relative humidity. Hence, disodium hydrogen phosphate containing between 0 and 20% moisture will have

Table 9.6 Characteristics of Disodium Hydrogen Phosphate

Type	Moisture in solid (%)		P_{H_2O}	Water activity (RH/100)
Anhydrous	0	Pair	9	0.38
Dihydrate	20	Pair	14	0.58
Heptahydrate	47	Pair	18	0.75
Dodecahydrate	60	Pair	22	0.92
Saturated solution (100 g water/4.5 g salt)				

Source: Maron and Prutton (1965).

above it an atmosphere of 38% RH. Similarly, as shown in the table, the heptahydrate contains 47% moisture, and mixtures of di- and heptahydrate give rise to water vapor pressures of 14 mmHg (58% RH). Similar plateaus exist for heptahydrate and dodecahydrate.

Two further points need to be mentioned: (a) If disodium hydrogen phosphate is stored at an RH between 38 and 58%, it will not pick up moisture (or will pick up only surface moisture). Once the relative humidity is raised to (slightly above) 58%, then it will start picking up substantial quantities of moisture until it has completely converted into the heptahydrate. (b) If the relative humidity is raised to (slightly above) 92% RH, then the dodecahydrate is converted to saturated solution. At higher RH values the equilibrium will be dictated by the water vapor pressure over the now unsaturated solution.

In the solubility plots there is always a nick in the curve at the point where there is a critical temperature. It is obvious that the heats of solution of two hydrate forms would be different, and this causes a different slope of the solubility curve. This is

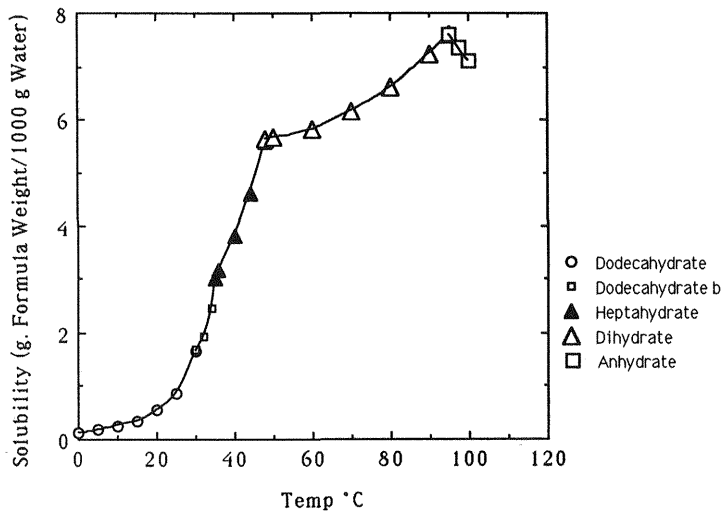


Fig. 9.17 Solubility of Na_2HPO_4 hydrates as a function of temperature. (Data from Brønsted, 1928.)

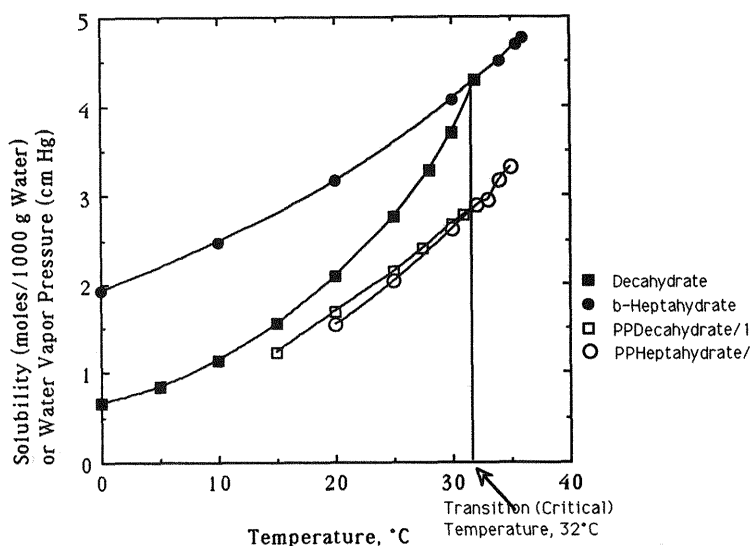


Fig. 9.18 Solubility and vapor pressure data of sodium carbonate hepta- and decahydrates. *PP* denotes vapor pressure curves in centimeters mercury. Solubility data (grams of solid per 100 g of water). (Data from Kracek, 1928.)

exemplified for the disodium phosphate system in Fig. 9.18. It is seen here (for the solubility curve of the anhydrate at higher temperatures), that solubility does not always increase with temperature. In this case the heat of solution is of a different sign so the solubility decreases with temperature. In general, however, there is a correlation between water vapor pressure and solubility of hydrates.

There are situations for which ΔH is not constant with temperature, but in solubility plots it often is. It is necessary to express the solubility in moles of solute per mole of solvent,

The situation is shown for sodium carbonate decahydrate and β -heptahydrate where both vapor pressure and solubilities are listed. It is seen that *the transition temperature (the critical temperature) is apparent (32°C) from both types of curve.*

9.12. MOISTURE EQUILIBRIUM CURVES OF A SMOOTH NATURE

It was mentioned earlier that compounds, such as gelatin, exhibit water vapor interactions that give rise to smooth (not stepwise) isotherms, and that these may be of a BET nature. If such a substance is evacuated and allowed to adsorb moisture up to a water activity close to unity, then a curve such as (a) in Fig. 9.19 will result. If the pressure is reduced again, then a curve will result that is different from the adsorption curve (a): desorption curve (b). This phenomenon is known as hysteresis. The ordinates will be denoted simply as x and y in the following.

It is noted that y_d is not an equilibrium condition. Obviously, ΔG is negative in going from the down-curve to the up-curve, because

$$\Delta G = V[P_u - P_d] < 0 \quad (9.40)$$

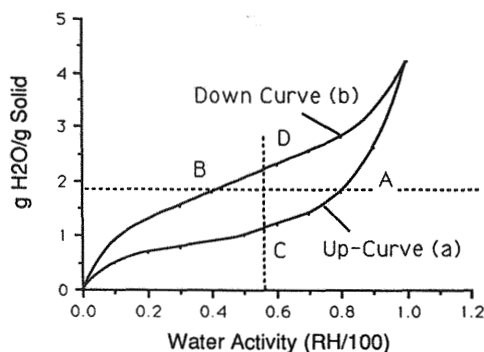


Fig. 9.19 BET adsorption and desorption moisture isotherm.

Several common tablet excipients give rise to Langmuir isotherms. In excipient study by Sangvekar (1974), when all the data are lumped together, they follow an equation of the type:

$$1/y = (A/P) + B \quad (9.41)$$

Usually, in pharmaceutical and engineering literature, the moisture equilibrium curves are shown in a sense opposite that shown in Fig. 9.19, that is,

$$P = \phi(y) \quad (9.42)$$

The high RH tail of the curve is usually above 85% RH and, therefore, is not applicable to most realistic pharmaceutical conditions, but it is applicable to one often-conducted test (40°C, 75%RH).

For routine isotherms, the high relative humidity tail is difficult to obtain with reasonable precision, and one approach (Carstensen, 1980) is to approximate them by Freundlich isotherms (i.e., not use the high end portion at all).

A solid dosage form (e.g., a tablet) is usually made to a given moisture content (e.g., 1.8 g/100 g of solid; Fig. 9.20). Because the drug and the excipients have different moisture isotherms, they will have different equilibrium RH values. There can, however, be only one RH condition in the pore space of the solid dosage form, so the result is that compound b will pick up moisture (move from B to D) and

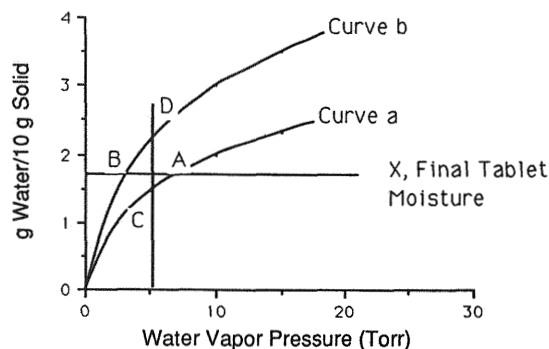


Fig. 9.20 Freundlich moisture isotherm presentation of initial part of a BET isotherm.

compound A will lose moisture (moving from A to C). The question is to estimate, quantitatively, where (at what RH) the line DC will be.

Two moisture equilibrium curves may (in an abbreviated fashion) be represented as Freundlich isotherms. This can be verified by inspection of Fig. 9.19, where lines OC and OB would both, fairly well, adhere to a Freundlich isotherm [Eq. (9.43)]:

$$y = qP^{(1/n)} \quad (9.43)$$

where q is a constant (Carstensen, 1980). This may be used to estimate the moisture movement in a solid dosage form after it is manufactured. If we consult Fig. 9.20 and assume that the up curve is that of drug (A) and the down curve that of excipient (B), there are m_A grams of A on an anhydrous basis, and A contains a fraction (on a dry basis) of q_A moisture (i.e., a total of $m_A q_A$ grams of water). There are m_B grams of B on an anhydrous basis, and B contains a fraction (on a dry basis) of q_B moisture (i.e., a total of $m_B q_B$ grams of water).

The dry weight of the dosage form, therefore, is $m_A + m_B$, and as the dosage form (e.g., tablet) is made, it is made at a particular moisture content of a fraction (on a dry basis) of q moisture (i.e., a total of $mq = [m_B + m_A]q$ grams of water).

Because, as seen from the figure, the relative humidity (the vapor pressure P) in the pore space must be one particular figure (P), it follows that A must give up moisture (from point A to point C) and B must take up moisture (from point B to point D).

The moisture isotherms are of the type

$$y(A) = y_A = q_A m_A / m_A = q_A = Q_A P_A^{1/n_A} \quad (9.44)$$

and

$$y(B) = y_B = q_B m_B / m_B = q_B = Q_B P_B^{1/n_B} \quad (9.45)$$

The values of n usually do not differ much (and the two isotherms, therefore, can be represented as differing only in the values of the Q 's). The areas have not been taken into account, and the isotherms apply to two samples of material (to account for the area, plotting by BET would have to be done).

In the situation for which a known amount of A m_A is mixed with a known amount of B m_B , mass balance (assuming no loss of moisture) gives:

$$y_C [m_A + m_B] = y_A m_A + y_B m_B \quad (9.46)$$

or:

$$y_C = (y_A m_A + y_B m_B) / [m_A + m_B] \quad (9.47)$$

and the amount of moisture lost can then be gauged from

$$\text{Moisture loss in A} = m_A (y_A - y_C) \quad (9.48)$$

and for B

$$\text{Moisture gain in B} = m_B (y_D - y_B) \quad (9.49)$$

As y_C is known, then P is also known.

If for instance the two compounds are mixed together, moisture added (as in a granulation), and this is dried, then x_C is known. Mass balance about ACB in Fig. 9.20 then gives that the moisture loss experienced by A

$$m_A(y_A - y_C) = m_A Q_A [P^{1/n} - P_C^{1/n}] \quad (9.50)$$

must equal the moisture gained by B:

$$m_B(y_D - y_B) = m_B Q_B [P_D^{1/n} - P_B^{1/n}] \quad (9.51)$$

All quantities are known, so that $P [= P_C = P_D]$ can be calculated (i.e., both moisture losses and gains, and the final relative humidity may be calculated). In this latter case, the isotherms should be determined on samples that have been wetted and dried the same way the final mix has been wetted and dried (because the surface area changes).

9.13. SOLVATES

What has been said in the foregoing also applies to the situation in which solvates are formed. In these, solvent (methanol, ethanol, or other) occupy sites in much the same fashion as water occupies sites in hydrates, and what has been said about vapor pressures also applies in this case, except it is now the vapor pressure of the solvent, not of water, that is of importance.

SYMBOLS

A = general symbol for a hydrate-forming compound

a = area of solid plus condensed liquid

B = $\pi\{[1 - FS]/Q\}^{2/3}$

BET = Brunauer, Emmett, and Teller

c = BET constant

d = diameter of particle after condensation

d_0 = diameter of particle before condensation

D = diameter of particle plus condensed water

E = $[FQ/(1 - FS)]^{2/3}$

h = thickness of adsorbed moisture layer

F = ρ^*/ρ

G = $k(P - P_s)B/3$

H = enthalpy

K = equilibrium constant

k = mass transfer rate constant

m = mass of one solid particle

N = number of particles

n = number of molecules (a) adsorbed, (b) dissolved

n_m = number of molecules in a monolayer

P_0 = water's vapor pressure at a temperature of T

P_a = water vapor pressure of vapor phase before condensation

P_s = vapor pressure over a saturated solution

P_{H_2O} = water vapor pressure

P_x = water vapor pressure of vapor phase after condensation

$Q = \rho^* N \pi / 6$

R = gas constant

RH = relative humidity

s or S = solubility of a compound in moles/mole of water

STP = standard pressure and temperature

T = absolute temperature, K

T^* = critical temperature for a hydrate

t = time

q = general symbol for a constant

V = (a) volume adsorbed; (b) volume of vapor phase

V_m = volume (STP) of adsorbate in a monolayer

w' = moles of water condensed

w = weight of water adsorbed per particle

W = weight of water dissolved per gram of solid

x = (a) mole fraction; (b) symbol for number of moles of water in a hydrate

x_s = volume fraction of solid in solution

z = moles of water per mole of solid for an unsaturated solution

y = (a) amount adsorbed; (b) mole fraction at saturation; (c) moles of water per mole of salt at saturation

ρ = density of liquid

ρ_0 = density of solid

ρ^* = density of solid plus adsorbate

REFERENCES

- Baxter AB, Lansing CD (1920). *J Am Chem Soc* 45:419.
- Bray ML (1999). *Pharm Dev Technol* 4:81.
- Brønsted JN (1928). In: Washburn EW, ed. *International Critical Tables*, vol 4. McGraw-Hill, New York, p 237.
- Brønsted JN (1943). *Fysisk Kemi*. Munksgaard, Copenhagen, pp 181–185.
- Carstensen JT (1986). *Pharm Technol* 9 (Sept):41.
- Carstensen JT, Danjo K, Yoshioka S, Uchiyama M (1987). *J Pharm Sci* 76:548.
- Chen LR, Grant DJW (1998). *Pharm Dev Technol* 4:487.
- Grant DJW, Medhizadeh M, Chow AHL, Fairbrother JE (1984). *Int J Pharm* 18:25.
- Jakobsen DF, Frokjaer S, Larsen C, Nieman H, Buur A (1997). *Int J Pharm* 156:67.
- Kracker FC (1928). In: Washburn EW, ed. *International Critical Tables*, vol 3. McGraw-Hill, New York, p 373.
- Maron SH, Prutton CF (1965). *Principles of Physical Chemistry*, 4th ed. MacMillan, New York, p 253.
- Partington AB, Winterton CD (1930). *J Chem Soc* 132:635.
- VanCampen L, Zografi G, Carstensen JT (1980). *Int J Pharm* 5:1.
- Zografi G, Hancock P (1993). *Int J Pharm* 10:1263.
- Zografi G, Kontny M (1986). *Pharm Res* 3:187.

This Page Intentionally Left Blank

10

Drug Substance Considerations

10.1	Salt Selection	160
10.2	Purification by pH-Change Precipitation	160
10.3	Precipitation Purification by Use of Mixed Solvent Technique	161
10.4	Purification by Thermal Recrystallization	162
10.5	Optical Isomers	163
10.6	Drying	164
10.7	Drying of Salt Hydrates	165
10.8	Dehydration Kinetics	167
10.9	Solvates	167
	Symbols	168
	References	168

It goes without saying that the drug substance is the most important part of a pharmaceutical solid-dosage form (except for placebos, and they are only important before the marketing of a drug product).

The syntheses of the drug is, therefore, the first step in development and discovery, and once a company decides to proceed with the development of a drug, there are a series of problems that are encountered and decisions that have to be made.

The actual synthesis of drugs is not the subject of this text, but there are aspects of it that have a direct bearing on further development.

Particularly, it is the purification of the raw chemical that is of importance. First of all, what chemical form (*salt form* for instance) is the one that should be pursued? What *recrystallization medium* should be used? Will these decisions have an influence on *polymorphism* or *hygroscopicity*?

These are problems that both the innovator and the generics encounter, because it is of importance to place specifications on the physical state of the drug substance. Other aspects, such as its *machinability* (i.e., whether it is easily made into tablets or capsules) should not be impaired.

10.1. SALT SELECTION

Drugs with ionizable functional groups are produced, most often, as specific salts (sodium salts, amine hydrochlorides, for example) and the reasons for using certain salts rather than the corresponding free bases or acids, include the following:

1. The base or acid may be an oil.
2. Most salts of acids have higher solubility than the free acids.
3. Salts most often crystallize more easily.

Clavulanic acid, which is a β -lactamase inhibitor used in Augmentin (SKB) is an oil, but its potassium salt is well defined. (The salt is also highly soluble; hence, it has a low critical humidity, a point that was discussed in the previous chapter).

High solubility is usually desired, but excessive solubility may be a drawback. High solubility usually results in bioavailability that is better than (or at least equal to) that of a less-soluble form, but excessive solubility causes higher hygroscopicity. It may also give rise to highly viscous, saturated solutions, and in this manner may impair the rates of solubility.

In general, drugs that have ionizable groups are prepared as either sodium or potassium salts; for drugs that contain carboxylic acids or those with an amine group, an addition salt, such as a hydrochloride may be used. For *amphoteric compounds*, there is the possibility of having either an addition salt, a free base or, for example, a sodium salt.

The sodium salt of amphoteric compounds are quite soluble, and hygroscopic. In such drugs a method of approaching formulation may be to employ the acid addition compound of the drug (the claimed substance) and neutralize it during wet granulation with sodium carbonate or sodium bicarbonate. The reaction is then brought to completion, and the tablet made. Examples of this are the sodium salt of enalapril, described by Sherman (1996a,b) in U. S. patent 5,573,780 and in moexipril (Gu et al., 1990) where this type of approach is described.

10.2. PURIFICATION BY pH-CHANGE PRECIPITATION

Purification is the final step of drug substance synthesis. Thermal recrystallization and precipitation are the most common methods of achieving purity. Sublimation is resorted to at times, but is not commonly used.

The precipitation may be accomplished in several ways. If the compound is a protolytic substance in solution, then a change in pH may be used for purification. An example of a compound that might be purified in this fashion is naproxen, because it has a solubility of 0.0159 mg/cm^3 and sodium naproxen has a solubility at 25°C of 196.7 mg/cm^3 in water at a pH of about 8 (Gu et al., 1990). If, for instance, 200 g of naproxen were added to approximately 1000 g of water at 25°C and made alkaline to dissolve it, and the pH then lowered to below 4, where free naproxen is the primary species, then $200 - 0.0159 \text{ g}$ would precipitate out. This

would be freed of any impurity that had a solubility higher than the final conditions would dictate.

If the naproxen used was not quite pure, but contained, for example, 1% of impurity, and if this impurity had a solubility in excess of 2 g/1000 g of water at pH 4, then 198 g of naproxen would precipitate and, theoretically, this would be free of the impurity.

If the impurity had a solubility of less than 2 g, for instance, 1 g/1000 g of water at pH 4, then 199 g of solid would precipitate, 198 g being naproxen and 1 g being impurity, so that the drug substance had been made purer (i.e., from containing 1% of impurity, it now contained only 0.5% impurity).

The purification process is, therefore, a function not only of the solubility profile of the drug substance, but also of the impurities. Adequate conditions (amount of water or other solvent, final pH) may be arrived at to optimize the purification.

The attainment of zero percent impurity by any form of precipitation method is ideal, rather than realistic. Adsorption will always occur, as well as occlusion.

Adsorption may be investigated research-wise, and most often Freundlich isotherms may be used to estimate gravity of impurity retention by adsorption. By the Freundlich equation, the amount adsorbed C^* , from solution is given by

$$\ln[C^*] = \ln q + n \ln[M] \quad (10.1)$$

where q is a constant and M is the amount in solution. In this manner it is possible to assess the severity of adsorption of different solvents and impurities.

10.3 PRECIPITATION PURIFICATION BY USE OF MIXED SOLVENT TECHNIQUE

If two solvents are miscible and the drug substance to be purified is soluble in one and poorly soluble in the other, then a precipitation by solvent change can be accomplished.

In the example in Fig. 10.1 the drug is soluble in water only to the extent of <0.02 mg/g of water, but is soluble in isopropanol to the extent of 3.9 mg/g of isopropanol.

If 3.9 g of drug substance is dissolved in 1000 g of isopropanol, and 4000 g of water then added, the solubility of the drug substance then drops to 0.02 mg/g of (mixed) solvent (i.e., a total of 5000 g of solvent is capable of dissolving only 0.1 g of drug substance), so that this water addition would allow 3.8 g of purer drug substance. The purity obtained will be a function of the level of impurities in the compound before reprecipitation and of their solubilities.

An example of the potential use of solubility in mixed solvents for precipitation purification was published by Jozwiakowski et al. (1996).

Residual solvent is a problem in precipitation purification. Residual solvent is removed by drying by heat or by vacuum (or by both). Microwave drying would work only if the energy frequency was adjusted to the particular solvent.

One situation that may arise is that the drug substance forms a solvate, and in this case, the ease of removal of solvent would depend on the equilibrium vapor pressure (at the drying temperature) of the solvent over the solid. Vacuum drying

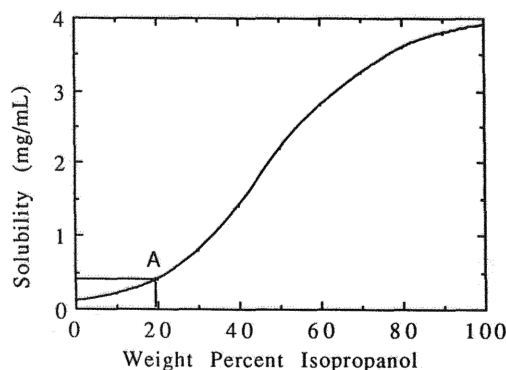


Fig. 10.1 Example of precipitation purification in water/isopropanol.

might be used to bring the pressure below that of the equilibrium vapor pressure of the solvent.

Residual solvent may also be the result of solvent entrapped in crystals as they precipitate (i.e., the solvent may occupy defect sites in the crystal). The best method of “freeing” solvent of this type is by way of comminution, because the milling may (a) expose the defect sites, or (b) make them sufficiently mobile to allow escape of the solvent.

The third situation is that surface removal of solvent forms an impenetrable crust, trapping solvent on the inside. This may happen when hard vacuum is employed, and in such a case, it may be corrected by using a lower vacuum and a longer drying time.

10.4. PURIFICATION BY THERMAL RECRYSTALLIZATION

This has, to a great extent, been covered in Chap. 6, but some comments at this point are of importance. As an example, assume that a compound is soluble to the extent shown in Table 10.1, and an impurity has the solubility characteristics shown.

Assume that a particular batch of the drug substance contains 2% of impurity (i.e., 98% of drug substance). Taking 10 g of the batch (i.e., 9.8 g of drug substance), adding to it 1000 g of solvent and heating it to 60°C will dissolve it all. By cooling it to 25°C, 9.5 g will precipitate out (under ideal, equilibrium conditions). The 0.2 g of impurity will present a concentration less than saturation (0.5 g/1000 g of solvent), and the precipitated drug substance will, theoretically, be “pure.” Because of adsorption and possible inclusion, this is never quite true, and limits on impurities, therefore, are always finite, not zero.

Table 10.1 Solubilities of a Drug Substance and an Impurity

Temp	Solubility of drug (g/1000 g of solvent)	Solubility of impurity (g/1000 g of solvent)
25	0.5	0.5
60	10	2

10.5. OPTICAL ISOMERS

A special case of purification is that of optical isomers. Compounds with one chiral center may occur as a *d*-form, an *l*-form, (denoted enantiomers), or (in a racemic compounds) as a *dl*-form. Equimolar mixtures of chiral compounds (denoted *dl*) may, depending on the compound in question, exist as racemic compounds or conglomerates. The expression *racemate* is often used, generically, to simply describe an equimolar composition of the two enantiomers without signifying whether it is a conglomerate or a racemic compound.

A racemic compound is, as the word implies, a compound, and may be considered as a strong complex between the two components. If the latter did not exist, then the mixture is a conglomerate (i.e., there is no chemical interaction between *d*- and *l*-forms) and, in that case, the solubilities of (excess amounts of) a mixture of a certain amount of the *d*-form and a certain (not necessarily the same) amount of the *l*-form would simply (approximately) be the sum of the solubilities of the two.

With the presence of a *d,l*-form the situation is, however, different. Dudu (1993) and Pudipeddi (1995) have reported on the isomers of pseudoephedrine. The solubility-phase diagram of this system is shown in Fig. 10.2.

It is noted in Fig. 10.2, when compared with a melting point phase diagram of a molecular compound to be treated shortly, that the solubility plot is exactly the upside-down inverse of the melting point plot. A situation similar to that of pseudoephedrine exists for dexamol hydrochloride (Liu and Hurwitz, 1978).

It is noted from Fig. 10.2 that the *dl*-form is less soluble than either of the enantiomers. "Chiral purity" appears to be mandatory for new drugs, and situations such as Fig. 10.2 makes separation by recrystallization impossible. A means of accomplishing it, however, is to derivatize the *dl*-compound with an optically active substituent. Here, the *d*-form derivative would have a different solubility than the *l*-form derivative, and fractional recrystallization can now be carried out. The resolved

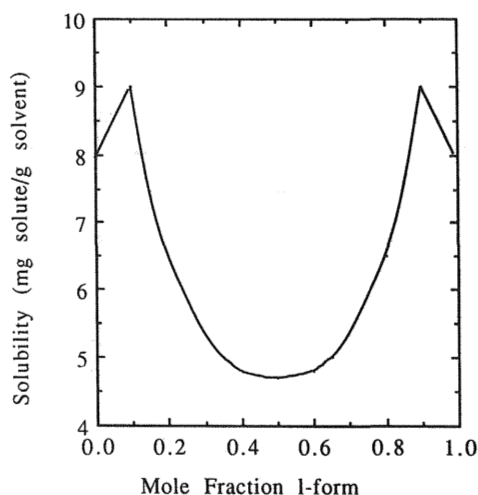


Fig. 10.2 Solubility-phase diagram of the pseudoephedrine system. (Data from Pudipeddi, 1995.)

enantiomer is then re-formed by dederivitization. This is tedious, costly, and yields are meager at times, and it adds to the cost of the drug. It is, however, often a necessity because of the toxicity of one enantiomer (the one not wanted).

In other cases, it is actually unnecessary (e.g., *dl*-tochopherol). But waiving the requirement for chiral purity seems to be only possible for "grandfather" drugs.

10.6. DRYING

After purification of a drug substance by recrystallization or reprecipitation, it is filtered or centrifuged to a certain degree of dryness, but a drying step is usually necessary.

For crystalline compounds that are not hydrates, drying is simply removal of surface moisture. Some pore space drying may occur (e.g., if agglomerates are formed). Micropores may also be dried out down to a certain pore size, but their moisture is often part of the residual moisture allowed by specifications. The manner in which specifications are set for moisture content is discussed in Chaps 14 and 15 dealing with stability.

If it is the drying of surface moisture, then the drying rate, dm/dt would be dictated by

$$q' = dm/dt = kA(P_0 - P) \quad (10.2)$$

where m is mass of water or other solvent, t is time, k is a mass-transfer coefficient, A is the surface area of the solid, P_0 is the vapor pressure of water or the solvent at the dew point of the airstream drying the solid, and P is the partial vapor pressure of water or the solvent in the drying airstream. A high k -value requires good heat and mass transfer such as in a fluid bed dryer or in spray drying. Equation (10.2) integrates to

$$m = m_0 - q't \quad (10.3)$$

where q is given by Eq. (10.2). The integration requires that A is (fairly) constant, which can be expected in most drying conditions. It also applies only to the phase where drying occurs, because once drying is complete, P is no longer the pressure at the dew point, but rather, the pressure at the temperature of the airstream. This allows drying to be monitored for the end point, for a rise in temperature of the exit airstream indicates that water or solvent has been completely removed (i.e., no more evaporation is taking place).

Some dry solids, such as zeolites or bentonites, contain internal water that dries by diffusion. The same holds true for amorphous solids. Drying of such drugs in general follows usual diffusion kinetics (Jost, 1960).

For simplicity, the solid particle will be considered spherical with a radius of r_0 . The initial, uniform concentration of water or solvent is denoted c_0 , and the final, uniform concentration is denoted c_∞ , and at time t the average concentration is denoted c . The expression for the average concentration c , at time t (Jost, 1960) is given by

$$(c - c_0)/(c_\infty - c_0) = Q/\pi^2 \sum_{i=1}^{\infty} (1/v^2) \exp[-v^2\pi^2 Dt/r_0^2] \quad (10.4)$$

where ν is a running index and where summation is with ν going from 1 to infinity. Q is a constant that is dependent on geometry (e.g., for a cylinder it is 6), but may be expressed by considering that at $t = 0$,

$$1 \approx Q/\pi^2 \sum_1^{\infty} (1/\nu^2) \quad (10.5)$$

so that

$$Q = \pi^2 \sum_1^{\infty} (1/\nu^2) \quad (10.6)$$

The term $(1/\nu^2) \exp[-\nu^2 \pi^2 D t / r_0^2]$ decreases drastically with increasing value of $1/\nu^2$ (e.g., it becomes four times smaller as ν increases from 1 to 2). Add to that the effect that increasing ν -values have on the term $\exp[-\nu^2 \pi^2 D t / r_0^2]$ and it is seen that quite an adequate approximation would be

$$(c_0 - c)/(c_0 - c_{\infty}) = Q/\pi^2 \exp\{-t/\tau\} \quad (10.7)$$

or

$$\ln\{(c_0 - c)/(c_0 - c_{\infty})\} = -\{t/\tau\} + \ln[6/\pi^2] \quad (10.8)$$

where

$$\tau = r_0^2/(\pi^2 D) \quad (10.9)$$

and where, depending on the geometry of the solid, Q may vary from 6 to 8. It is noted that the approximation gives some zero time deviation from intercept with zero for Eq. (10.3) (Pitkin and Carstensen, 1973). To convert Eq. (10.2) to mass of water or solvent, m , in a particle, rather than concentration within a particle, it is necessary to multiply by the volume V , and if it is assumed that the final amount of water or solvent, $m_{\infty} = 0$, Eq. (10.9) becomes

$$1 - (m/m_0) = \exp(-t/\tau) \quad (10.10)$$

The left-hand side is the fraction (or if multiplied by 100, the percentage) of moisture left at time t .

This shows that the drying process in a diffusional phase is loglinear in time, and shows that it is the more rapid, the smaller the particle. The effect of geometry is such that the factor $(A/\pi)r_0$ most often is close to unity.

Usually, drying curves are separated into the three sections shown in Fig. 10.3: (a) drying of surface moisture (the linear drying phase), (b) drying by diffusion (the falling-rate phase), and (c) overdrying. Overdrying is particularly directed toward drying of hydrates, as shall be discussed in the next section.

10.7. DRYING OF SALT HYDRATES

As mentioned in Chap. 9, the water in hydrates is partly held in the coordination shell about the ions in the lattice, and partly it occurs as *structural* water. The

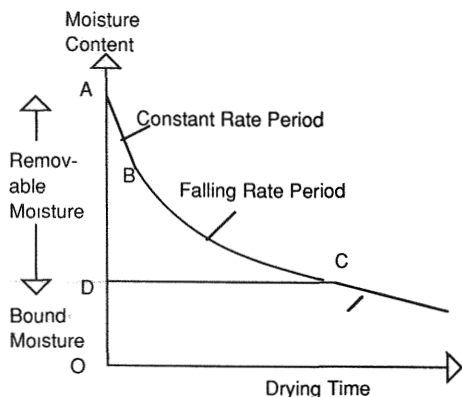


Fig. 10.3 The different drying phases.

structural water is held much less tightly than the coordination water. For instance, $\text{MgCl}_2 \cdot 4\text{H}_2\text{O}$ fails to give up the last two molecules of water when heated above 120°C , but rather gives off HCl . In the following, the “drying” of the hydrate is considered to be twofold, depending on purpose. Either it is desirable to remove the surface moisture and not the water of hydration, or (b) it is desired to remove the (structural) water of hydration.

It is apparent from the previous chapter that at any given temperature below the critical temperature T^* of a salt hydrate, there is the possibility of removal of water (or solvent) of hydration. Often (e.g., ampicillin, amoxicillin, and cephalosporins), it is the salt hydrate that is the desired form of the drug substance, but on the other hand, adsorbed moisture may be deleterious to the compound as well as dehydration of the hydrate.

Drying with airstreams with a relative humidity equaling that of the equilibrium relative humidity of the salt hydrate will remedy that, but on the other hand, drying is more rapid if lower humidities or higher temperatures are used. The finesse, then, is to stop the drying at the right point.

Drying, at times, causes undesired effects, depending on drying conditions. Sucrose, for instance (Zoglio et al., 1975) forms an, at times water-impenetrable, crust during fluid bed drying under some conditions.

Vacuum drying causes similar crusts to form (Garner, 1953) in the case of copper sulfate pentahydrate and magnesium tartrate dihydrate. In vacuum drying it is often advantageous not to employ a hard vacuum, as shown in Fig. 10.4. In the cited cases (Fig. 10.5), X-ray examination of the dried compound has demonstrated that vacuum drying forms a skin possessing no crystalline structure, whereas drying in moister atmospheres does not give rise to this phenomenon. In the hard vacuum, moisture evaporates off of the surface, creating an anhydrous ionic network, which is unstable (except for zeolites). It is unstable in that it rearranges to a phase that has no well-defined crystallinity (see Fig. 10.5, phase B). This further nucleates (see Fig. 10.5, phase C), a process that is accelerated by the presence of water. This nucleation and crystallization gives cracks at right angles to the interface. The drying then takes place through a continuous layer (B) and a reduced surface (the cracks in C).

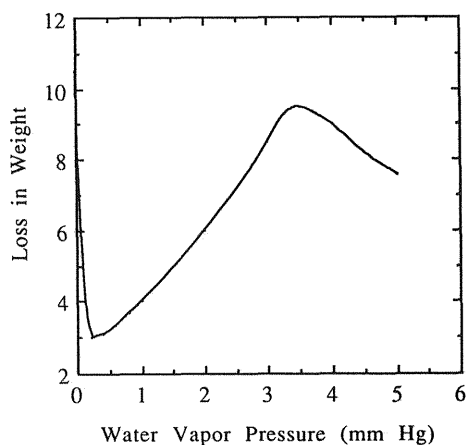


Fig. 10.4 Drying rates of $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$ as a function of water vapor pressure.

10.8. DEHYDRATION KINETICS

Taylor and York (1998) studied the dehydration of trehalose dihydrate, and found that none of the conventional equations would fit the dehydration data well.

10.9. SOLVATES

It is not only water that may become part of the lattice of a compound. Solvents (ethanol, methanol, and such) may also occupy lattice sites, and in that case, one talks about solvates.

Pohlman et al. (1975), for instance, have shown that at least three polymorphs exist of carbamazepine, the first being monoclinic (Reboul et al., 1981, Himes et al., 1981), the second one being trigonal (Lowes et al., 1981). The structure of a dihydrate

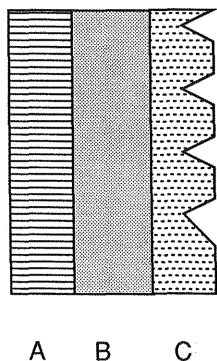


Fig. 10.5 Hard vacuum drying of CuSO_4 (A) causes an amorphous, anhydrous subphase (B) that then crystallizes to a phase (C) containing cracks. Drying is impaired by the moisture first having to penetrate layer B, and then being able to escape only through narrow cracks.

(Reck and Dietz, 1986) and that of an acetate (Terrence et al., 1983) have also been reported.

SYMBOLS

- A = surface area of the solid
 C^* = amount in solution in equilibrium with a solid of concentration M
 c = average concentration of water (or solvent) in a particle being dried
 c_0 = value of c at time zero
 c_∞ = value of c after drying is complete
 D = diffusion coefficient of water (or solvent) through a solid
 k = mass transfer coefficient
 M = (a) amount adsorbed (Freundlich equation), (b) molecular weight
 m = mass of water or other solvent in a solid being dried
 m_0 = original mass of water in a solid being dried
 n = exponent in the Freundlich equation
 P_0 = water (or solvent) vapor pressure at dew point
 P = water (or solvent) vapor pressure
 Q = coefficient in drying equation, depending on shape
 q = constant in the Freundlich equation
 q' = drying rate constant in the constant rate drying period
 r_0 = radius of a spherical particle being dried
 T^* = critical temperature
 t = time
 ν = running index
 $\tau = r_0^2/(\pi^2 D)$ = unit that reduces drying time to reduced, nondimensional time

REFERENCES

- Duddu SP (1993). PhD dissertation, University of Minnesota, Minneapolis, MN.
 Gu L, Strickley RG, Chi L-H, Chowhan ZT (1990). *Pharm Res* 7:379.
 Himes VL, Mighell AD, DeCamp WH (1981). *Acta Crystallogr B* 37:2242.
 Jost W (1960). *Diffusion in Solids, Liquids, Gases*, 3rd printing. Academic Press, New York, p 46.
 Jozwiakowski MJ, Nguyen N-T, Sisco JJ, Spankac CW (1996). *J Pharm Sci* 85:193.
 Liu S, Hurwitz A (1978). *J Pharm Sci* 67:636.
 Lowes MMJ, Cairfa MR, Lötter AP, Van Der Watt JG (1987). *J Pharm Sci* 76:744.
 Pitkin C, Carstensen JT (1973). *J Pharm Sci* 62:1215.
 Pudipeddi M (1995). PhD dissertation, University of Wisconsin, Madison, WI, p 77.
 Pohlman H, Gulde C, Jahn R, Pfeiffer S (1975). *Pharmazie* 30H.11:709.
 Reboul JP, Cristau B, Soyfer J-C, Astier J-P (1981). *Acta Crystallogr B* 37:1844.
 Reck G, Dietz G (1986). *Cryst Res Technol* 21:1463.
 Sherman BC (1960a). U. S. Patent 5,573,780.
 Sherman BC (1960b). U. S. Patent 5,573,962.
 Taylor LS, York P (1998). *Int J Pharm* 167:215.
 Terrence CF, Sax M, Fromm GH, Chang C-H, Yoo C (1983). *Pharmacology* 27:85.
 Zoglio MA, Steng WH, Carstensen JT (1975). *J Pharm Sci* 64:1869.

11

Melting Point Diagrams and Eutectics

11.1.	Freezing of Ideal Solutions and Ideal Solubility	170
11.2.	Melting Point Depressions and Purity Assessment by the Van Laar Equation	171
11.3.	Eutectic Diagrams	172
11.4.	Molecular Compounds	174
11.5.	Solid Solutions	175
11.6.	Hydrous Amorphates	176
11.7.	Lyophilization: Amorphous Cakes	176
11.8.	Immiscible Melts	178
11.9.	Miscible Melts	179
11.10.	Solid Solutions of the First Kind	182
11.11.	Partially Miscible Melts	183
11.12.	The Separated Phase: Solid Solutions of the Second Kind	184
11.13.	Melts	184
11.14.	Coprecipitates	185
11.15.	Cogrinds	186
11.16.	Dissolution of Solid Dispersions	186
	Symbols	187
	References	187

11.1. FREEZING OF IDEAL SOLUTIONS AND IDEAL SOLUBILITY

Before discussing melting point diagrams, a note on ideal solubility relations is in order. Assume that a crystalline substance *A* is dissolved in water, and assume that the two do not form solid solutions. If a plot is made of the mole fraction x_s at which one or the other solid phase (ice or drug) is in equilibrium with a solution, then a diagram such as shown in Fig. 11.1 results.

If cooling is carried out from composition *S*, then there will be a separation of ice at a temperature of *R*, and in similar fashion a solution of composition *V* will precipitate drug at point *Q*. It is assumed that the separated phases are crystalline. The freezing point trace of water is the section *NU* and at the other side of point *U* the curve *UQ* is denoted the solubility curve of *A*. It is noted (as opposed to conventional eutectic diagrams) the curve is not continued all the way to the right *y*-axis, because an upper temperature (e.g. the boiling point of water) is usually indicated (composition *W*).

The condition of equilibrium is that the chemical potentials of the solute in solid and dissolved form, μ_s and μ_b are the same. We may write

$$\mu_s = \mu_b \quad (11.1)$$

but

$$\mu_b = \mu_b^* + RT \ln[a] = \mu_b^* + RT \ln[x] \quad (11.2)$$

since for an ideal liquid, *a* may be substituted by *x*, the mole fraction. μ_b^* is then the standard chemical energy of a solution of a mole fraction of unity.

This may be rearranged to read

$$\ln[x] = -\{\mu_b^*/[RT]\} + \{\mu_b/[RT]\} \quad (11.3)$$

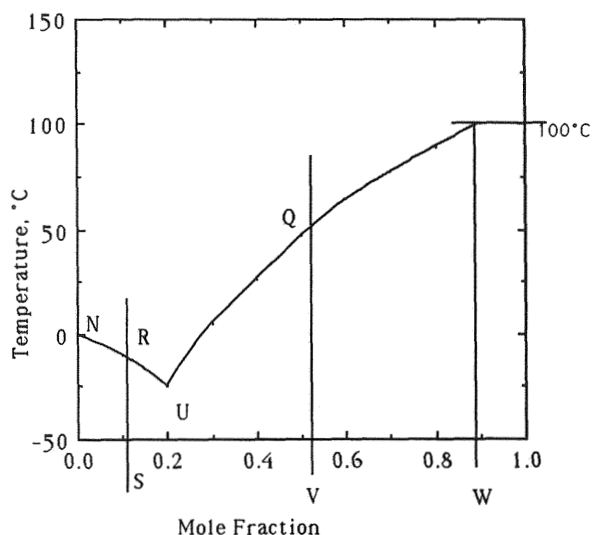


Fig. 11.1 Freezing point diagram of a solid and water.

The temperature dependence of x may be written (and expanded by Eq. 11.1)

$$\begin{aligned}\{\partial \ln[x]/\partial T\}_P &= -\{(1/R)\{\partial(\mu_b^*/T)/\partial T\}\} + \{(1/R)\{\partial(\mu_b/T)/\partial T\}\} \\ &= -\{(H - h)/RT^2\}\end{aligned}\quad (11.4)$$

The notation H is for partial molar heat of the solid compound in ideal solution and h denotes enthalpy of the pure solid per mole, both at a temperature of T . By introducing the concept of the heat absorbed, L , at constant pressure and temperature, Eq. (11.4) may be recast as

$$\{\partial \ln[x]/\partial T\}_P = L/RT^2 \quad (11.5)$$

For the left side of the freezing point diagram, this equation is known as the freezing point equation, and at the right-hand side of point U it is the solubility equation of B in the liquid A (e.g., water).

11.2. MELTING POINT DEPRESSIONS AND PURITY ASSESSMENT BY THE VAN LAAR EQUATION

Integration of Eq. (11.5) gives rise to the Van Laar equation, which allows assessment of the purity of a drug substance by obtaining its "melting point" T . For the part of the diagram in Fig. 11.1 to the left of U , the separating phase is water, and the mole fraction of water, with the terminology used, would be $(1 - x)$. If the impurity constitutes a mole fraction x and the melting point of the pure drug substance is T_0 K, then the melting point of the contaminated drug substance T K, is given by:

$$\ln[1 - x] \approx -x = -\Delta H/R\{(1/T) - (1/T_0)\} \quad (11.6)$$

or

$$x = \Delta H/R\{\Delta T/T_0^2\} \quad (11.7)$$

R is the gas constant and ΔH the heat of fusion.

It is common to employ differential scanning calorimetry (DSC) for this type of determination, and it is possible, in so doing to construct the "eutectic curve" in its entirety. For instance if ΔH equaled 8000 cal/mol and T_0 were 200°C, it is possible to develop the entire melting point curve as follows:

T is calculated for several of x -values by using Eq. (11.6). A program to achieve this is shown in Table 11.1.

Equation (11.6) may be written:

$$(1/T) = (1/T_0) - (R/\Delta H)\ln(1 - x) \quad (11.8)$$

The program gives x up to 0.6, but can be extended by changing the upper limit in the FOR-TO statement to 1.0. Most eutectics have intersections in "the middle."

Inserting, for instance $\Delta H = 8200$ and $T_0 = 190$ gives the results in Table 11.2. A similar program may be written for the right-hand side of the diagram (by substituting $(1 - Y_1)$ for Y_1 and rewriting the appropriate lines.

It is noted that although x may be determined in this fashion, it gives no information about what the contaminant is and, hence, not knowing its molecular weight, the value of x cannot be translated into weight percent.

Table 11.1 Program for Eq. (11.8)

```

INPUT "HEAT OF FUSION=";Q1
INPUT "ELT.TEMP.°C=";F1
FOR Y1 = 0 TO .6 STEP .1
F2 = F1 + 273.15
F3 = 1/F2
Y2 = 1.99/Q1
Y3 = LOG(1-Y1)
Y4 = Y2*Y3
Y5 = F3-Y4
Y6 = 1/Y5
Y7 = Y6-273.15
PRINT Y1,Y7
NEXT Y1

```

The eutectic point is rarely a rational fraction and is, in essence, the intersection between two solubility curves.

The most common way to assess impurities in preformulation is by the use of DSC. A schematic of a DSC trace is shown in Fig. 11.2.

11.3. EUTECTIC DIAGRAMS

A literature example (Giordano et al., 1998) of a eutectic diagram is shown in Fig. 11.3. In this figure the melting points of mixtures of piroxicam pivalate (PIRP) (polymorph I) with piroxicam (PIR) are shown. A melt at 170°C of 0.12 mol fraction PIR will start "freezing" (showing separation out of a solid phase) at 150°C. The solid phase is PIRP and, depending on the rate of cooling, the crystals formed are or can be fairly large (in a relative sense). As the temperature decreases, there will be more PIRP precipitating out, and the liquid (melt) with which is in equilibrium is given by the corresponding composition of the liquidus line. At point *C* the following occurs: if one considers the lines *AC* and *DC* solubility curves, it follows that lowering the temperature below 140°C will cause supersaturation of both com-

Table 11.2 Results from Table 11.1 Using $\Delta H = 8200$ cal/mol and $T_0 = 190^\circ\text{C}$

Mole fraction x	Melting point
0	190
0.1	184.6
0.2	178.7
0.3	172.1
0.4	164.9
0.5	156.5
0.6	146.8

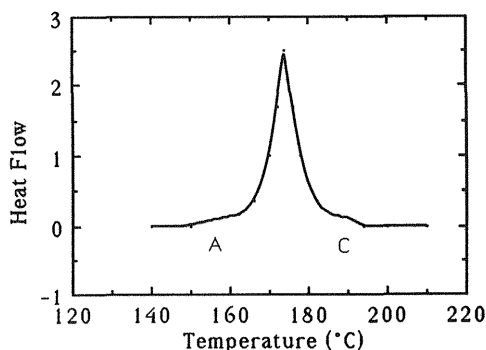


Fig. 11.2 Schematic of DSC trace of compound containing an impurity.

pounds; therefore, precipitation of both will occur. Because supersaturation will cause precipitation of small particles, the *eutectic mixture* will precipitate out (solidify) as a finely divided mixture of PIRV and PIR, in addition to the coarser PIRP already precipitated. Similar considerations apply for cooling along the line JH , except here it is PIR which constitutes the coarser part, which precipitates out before the eutectic precipitation.

The eutectic composition is *not* (necessarily) a rational ratio between the two compounds, and is not to be considered a “compound.”

Below line BHE (the eutectic temperature) only solid phase exists, and above line ACD only liquid (melt) exists. The area ACB consists of PIRP plus melt, and the area CDE is an area where PIR plus melt exists. C is denoted the eutectic composition.

Heating solid along composition x_F or x_H will cause an onset of melting at temperatures T_F (or T_H), and at temperatures between T_F and T_G (or between T_H and T_J), there will be two phases present. In the former, solid PIRP and a liquid consisting of a mixture of PIR and PIRP. The liquidus line is essentially a line indicating the solubility of PIRP in molten PIR at the given temperature.

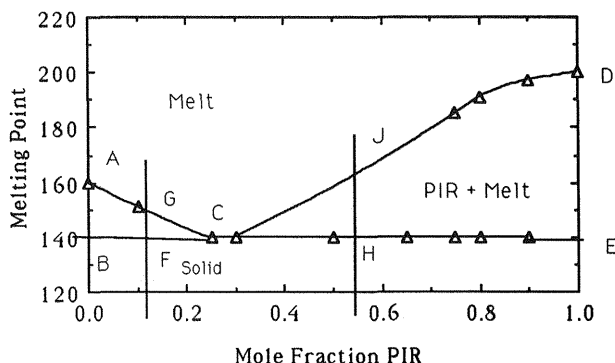


Fig. 11.3 Binary phase diagrams of piroxicam pivalate (polymorph I) with piroxicam. (Data from Giordano et al., 1998.)

Similarly, the line CJD is the solubility–temperature line of PIR in molten PIRP. In the latter, the solubility (in mole fraction) is $(1 - x)$.

The diagram is established by DSC, and the eutectic temperature is the onset of the endotherm, and the complete “melting” temperature, T_G or T_J as the end of the endotherm.

By knowing the value of ΔH_I and ΔH_{II} of the two polymorphs I and II of PIRP at their at their melting points allows calculation of one leg of the eutectic diagram, and knowing ΔH of PIR at its melting point then allows calculation of the other leg. Giordano (1998) from this (according to Yu, 1995; Burger and Ramber, 1997) calculated $x_{E1} = 0.26$, $T_{E1} = 140.7$ K, $x_{E2} = 0.18$, $T_{E1} = 128.5$ K. Assuming ΔG to be proportional to T allowed them to calculate the transition temperature to be 32°C and to establish the Gibbs energy diagram.

11.4. MOLECULAR COMPOUNDS

In certain instances the binary melting point between two compounds will have an appearance as shown in Fig. 11.4. One may think of the diagram consisting of two adjacent, simple eutectic diagrams. The compounds, in that case are A and $[A_xB_y]$ for one and B and $[A_xB_y]$ for the other, i.e., $[A_xB_y]$ where x and y are simple numbers, is a chemical compound.

Hildebrand and Müller–Goymann (1997) have reported on mixed crystals of ketoprofen and its sodium salt. Ketoprofen (DSC) shows a melting endotherm with onset at 352 K and a mixed crystal onset of 400 K. If the molecular compound were equimolar, then the first peak should not have occurred. Hildebrand and Müller–Goymann studied mixtures of the acid and sodium salt in various ratios and then found three peaks, with a local maximum in enthalpy of fusion at about 33% ketoprofenic acid. This would imply a molecular compound of two sodium salts to one acid. To demonstrate this experimentally the authors prepared sodium salt/acid in the ratio of 2:1, and the crystals thusly formed exhibited only one melting peak at 422 K. X-ray and scanning electron microscopy (SEM) showed these crystals to be

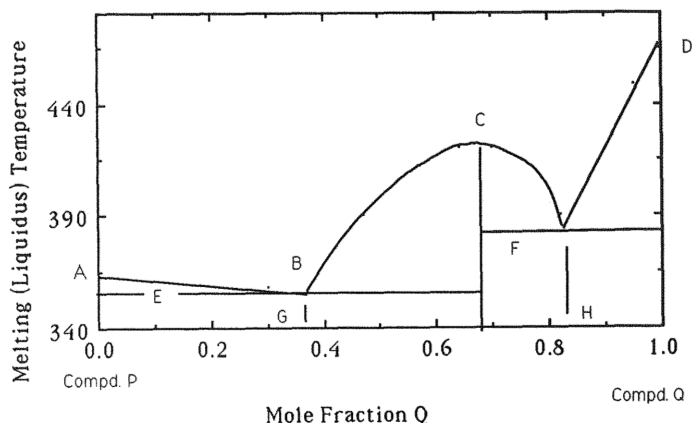


Fig. 11.4 Binary melting diagram with molecular compound formation. (Data from Hildebrand and Müller–Goymann, 1997.)

quite different from either sodium salt or acid. It is noted that the point C should happen at a rational composition (1:1, 1:2, 2:3, 1:3).

The foregoing is distinguished from *solid dispersions*, which will be discussed in Sec. 11.14. It is also noted that Fig. 11.4 is the (horizontally flipped) mirror image of Fig. 10.1, showing the close relation between solubility and melting point diagrams.

11.5. SOLID SOLUTIONS

In certain instances two solids can form homogeneous, solid mixtures; therefore, such solids may be thought of as solutions. It is difficult to establish equilibrium in such solutions, and, consequently, measurements are quite uncertain (Frazer, 1931). The binary melting diagrams, for solid solutions may have one of the shapes shown in Figs. 11.5 and 11.6.

In the foregoing examples, the situation has been depicted in which the phase that separates out on freezing is one of the pure components (i.e., there is no mutual solubility between A and B), to the left of C in Fig. 11.3, it would be A to the right it would be D.

There are compound pairs when one compound A has a limited solubility in the other B and, here, solid solutions occur (i.e., the phase that separates out is not pure A or B, but is A with some B or vice versa). Three of the possible situations are shown in Fig. 11.5

The upper curve is denoted the *liquidus* line as in the foregoing, and the lower curve is denoted the *solidus* line. In case (a) each component decreases the melting point of the other, in case (b) one increases and the other decreases, and in case (c) both increase. It is tempting to think of point b in case (a) as a eutectic point, but it is not.

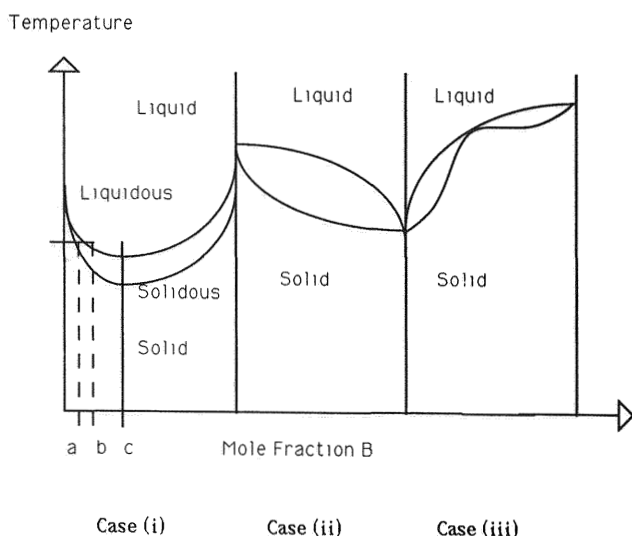


Fig. 11.5 Three situations in which solid solutions occur.

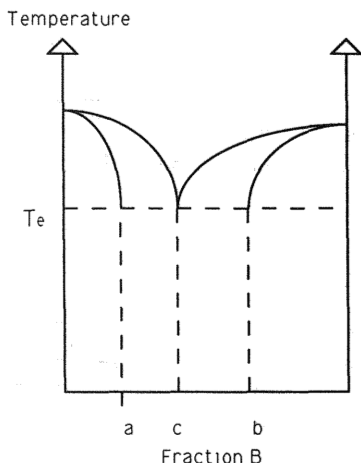


Fig. 11.6 Binary melting point diagram for two compounds, A and B, which form solid solutions *and* an eutectic.

These systems have not been frequently reported in the pharmaceutical literature (but have been reported in the metallurgical literature). Some reports in the pharmaceutical literature have dealt with systems of the type shown in Fig. 11.6. In this instance the point c is, indeed, an eutectic point, but the (finely subdivided) solid phases that separate out are of compositions a and b, not of pure compounds A and B.

Such systems have been reported for pharmaceutical systems by (Sekiguchi and Obi, 1961; Sekiguchi et al., 1963, 1964a; Goldberg et al., 1965; Guillory et al., 1969; Chiou and Niazi, 1971). Carstensen and Anik (1976) have reported on the proportional requirements that must be met for a solid solution composition to occur.

11.6. HYDROUS AMORPHATES

Solids that are not crystalline are denoted *amorphous*. An important category of this is lyophilized cakes (for intravenous reconstitution). These are formed by freezing aqueous solutions. On such freezing (when part of the solid comes out as an amorphate), ice will first freeze out, and then the remaining solution (which under other conditions might crystallize as a eutectic), will supercool and will become "solid." But here the "solid" is simply a very viscous solution. An example of this is Fig. 11.7 (Her and Nail, 1994).

In practice this usually refers to lyophilized cakes. The glass transition temperature can usually be arrived at from thermal analysis, as shown in Fig. 11.8.

11.7. LYOPHILIZATION: AMORPHOUS CAKES

The *solid* in freeze-drying is (when dried) referred to as a lyophilized cake. It is mostly amorphous, and the glass transition temperature can be arrived at from thermal analysis (see Fig. 11.8). The collapse temperature in Fig. 11.8 is a temperature dictated by mechanical properties. Just above the glass transition temperature,

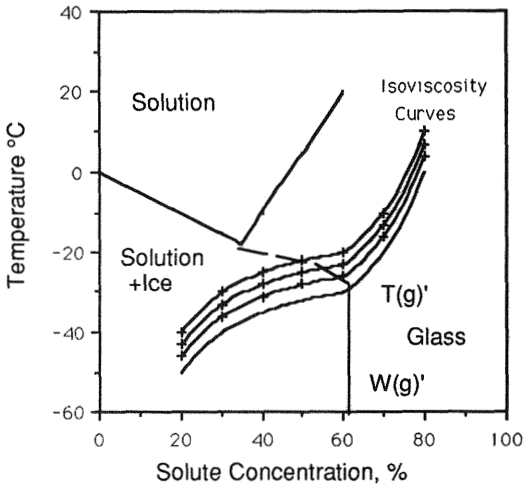


Fig. 11.7 An example of a supercooled viscous solution. (Data from Her and Nail, 1994.)

sucrose solutions, for instance, have viscosities of about 10^6 Pa/s, but below T_g this figure is 10^{12} Pa/s. The general sequence of events in freeze-drying is shown in Fig. 11.9.

The primary drying (see Fig. 11.9) consists of the evaporation of the crystalline ice, so that the cake is left with “holes” in it, and a glass of a water content in the range of 12–15% results. If the temperature is below the glass transition temperature, then this glass has a high viscosity and will dry slowly, because the diffusion coefficient D for evaporation of water, will be high.

If, after the primary drying, the initial freezing temperature is 240 K (Fig. 11.10) and the solids content is 50%, then the composition would be at point C, between the T_c and T_g curve. But if sublimation were continuously carried out at this

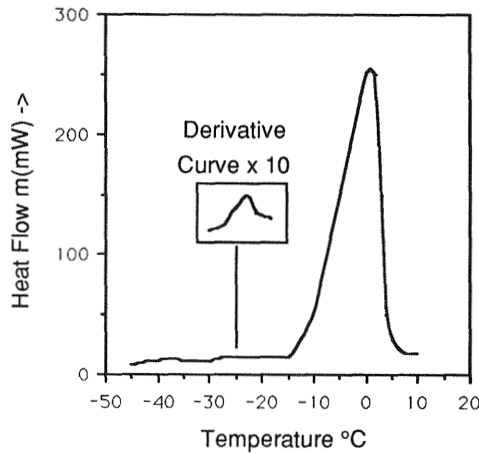


Fig. 11.8 Thermogram of aqueous solution of 10% PVP. The relative magnitudes of the endotherms for glass transition vis-a-vis melting is shown. (Data from Her and Nail, 1994.)

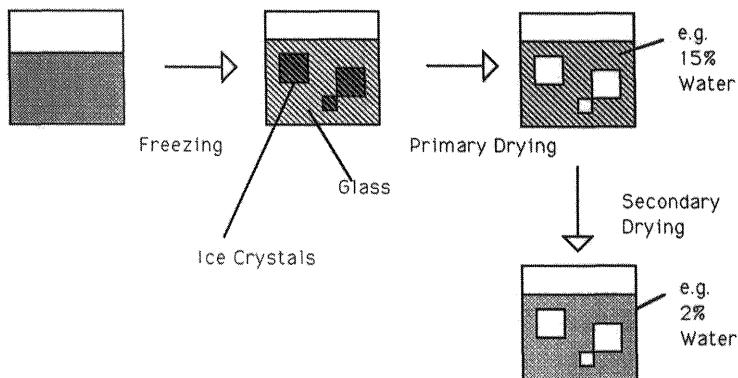


Fig. 11.9 Schematic of freeze-drying events.

temperature, then, at point *B*, the glass transition would be passed, and the viscosity would become very high, and sublimation would be very slow. The temperature, therefore, is continuously increased, such that the lyophilization temperature can stay within the bounds of the two curves.

Some proteins have stabilities that depend on cooling rate, but this is primarily due to electrolytes (e.g., sodium chloride) and stabilizers (e.g., glycine) in the composition. These will crystallize out and give the cake structural strength, such that T_C increases, but their presence, as well as the initial freezing rate, will modify the positions of the two curves, so that a slow-cooling rate may provide a different (and sometimes worse) curve than when a fast-cooling rate is employed.

These aspects have been discussed in detail (Franks, 1990; Levine and Slade, 1988; MacKenzie, 1977; Suzuki and Franks, 1993).

Turel et al. (1997) have shown that the water in ciprofloxacin is present in a complicated hydrogen-bonded network.

11.8. IMMISCIBLE MELTS

Eutectics have been treated, in an initial sense, in the foregoing, and this is of interest whenever a binary or multinary system is melted. As the heading implies, there is a

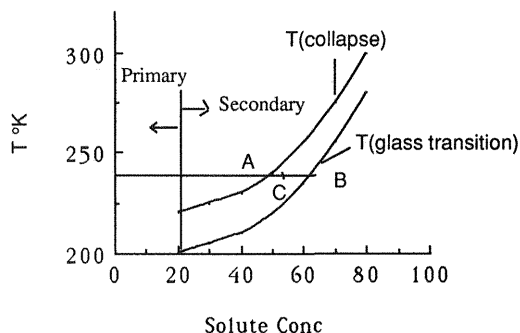


Fig. 11.10 Limiting phases in a lyophilization event.

series of different systems that may arise. The systems are considered binary in the following chapter, and the components are denoted A and B. It is assumed in the following that A has the lower melting point.

If two substances, A and B, are mixed, and if their melts are totally immiscible, then heating a solid mixture of the two will first result in A melting, producing a suspension of B in molten A. Then, on further heating, B will melt, and the two liquids will be immiscible (i.e., form two phases).

A DSC thermogram of such a mixture would simply show a sharp-melting point for A, followed by a sharp-melting point for B. Systems of this kind are rare and are not of much practical interest, other than serving as an introduction to the concepts to follow. However, mixtures of inorganic electrolytes (sodium chloride) and organic materials would be of that ilk, but the experiment described would be a theoretical exercise, because most organic materials decompose at or before the temperatures at which inorganic electrolytes melt.

11.9. MISCIBLE MELTS

The commonly referred to situation of eutectic diagrams is the one shown in Fig. 11.11 (which is repeated for convenience). The melting point of a mixture decreases from the pure compound; for example, if a mixture of A and a little B are melted (point U), and then cooled along the line CQ, then solid phase will separate out when the temperature at C is reached.

This “precipitate” may be fairly coarse. As the cooling progresses (e.g., to the temperature corresponding to point W), more and more solid will have precipitated (separated) out, and the liquid will become richer and richer in B. At point W, the liquid composition will be X, and the amount of liquid, m_L , versus the amount of solid m_s , is given by the so-called weight arm rule:

$$\{VW\}m_s = \{WX\}m_L \quad (11.9)$$

If the composition at U is denoted x and the composition at point X is denoted x_L , then Eq. (11.9) translates to

$$xm_s = (x_L - x)m_L \quad (11.10)$$

If this is divided by the total mass ($m_s + m_L$), then Eq. (11.10) becomes:

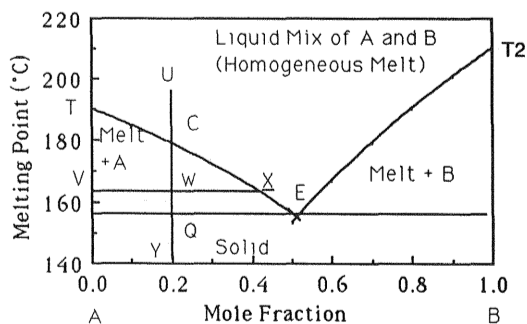


Fig. 11.11 Eutectic diagram.

$$xf_s = (x_L - x)f_L = (x_L - x)(1 - f_s) \quad (11.11)$$

where f_s is the mass fraction of solid and f_L is the mass fraction of liquid.

When the point E (the eutectic point, corresponding to the eutectic temperature and the eutectic composition) is reached, then the following dilemma occurs: Line TE , the so-called *liquidus line* represents the solubility curve of B in A. (The line ET_2 is the other liquidus line and represents the solubility of A in B). If the temperature were to drop below the eutectic temperature, then the solubility of A in B and the solubility of B in A would be superseded. In an *equilibrium* situation, this cannot occur, so that the situation is resolved in nature by both A and B precipitating.

It follows from the type of situation that large crystals of either would not be possible (would result in too large an increase above solubility of either compound), so that what will happen at further cooling (i.e., removal of heat) is that a very finely subdivided mixture of A and B, the *eutectic mixture* will occur. As this precipitation occurs, *removal of heat will not result in a reduction in temperature*. Not until the entire mass has frozen will the temperature drop again.

Along the line $UCWQY$ in Fig. 11.11 the temperature profile, assuming constant heat removal, would be as shown in Fig. 11.12(a) and at the eutectic composition, $x(E)$ it would have the appearance in Fig. 11.12(b). The latter profile is exactly the same as for a pure compound, but for a eutectic, $x(E)$ would not be a convenient ratio (1:1, 1:2, 1:3, for instance).

The conventional eutectic diagram, with soluble liquid phases, divides the space into four areas, as shown in Fig. 11.11. The area above the line TET_2 , where the system is liquid, the area below the line QE where the system is solid, consisting of coarse crystals of one of the components and a "eutectic mix" of finely subdivided crystals of A and B, and the two triangular areas where the system consists of melt plus A or melt plus B. If it were melt plus A plus B, then the number of phases p would be four (including vapor), and by Gibbs' phase rule the degrees of freedom n , would be given by

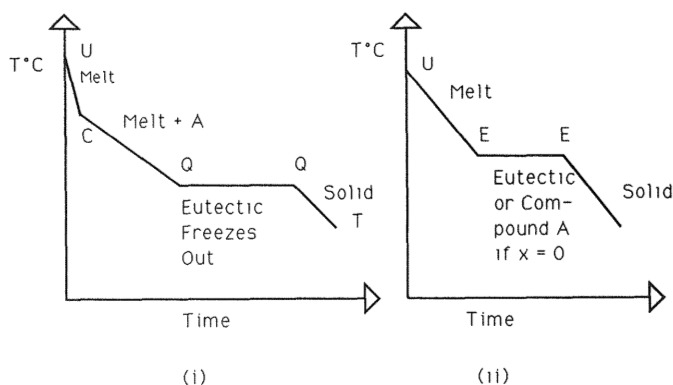


Fig. 11.12 Temperature profile during cooling along line $UCWQY$ in Fig. 11.11. (a) represents cooling of a noneutectic composition, whereas (b) is either one of the pure compounds ($x = 0$ or $x = 1$) or the eutectic composition [i.e., $x = x(E)$ in Fig. 11.11].

$$n = f - p + 2 = 2 - 4 + 2 = 0 \quad (11.12)$$

where f , the number of components, is 2. This means that temperature cannot be changed if both A, B and melt are present, and this is exactly the situation depicted by Fig. 11.12.

The lines TE and T_2-E are solubility curves, where the solubility is expressed in mole fraction. The solubility equation for section TE would be

$$TE: \quad \ln(1 - x_B) = -\{\Delta H_A/RT\} + \beta_1 \quad (11.13)$$

where ΔH_A is the heat of fusion of A, x_B is the mole fraction of B, R is the gas constant, T is absolute temperature, and β_1 is a constant applying to B in the system.

For the section $E-T_2$ the same type equation applies:

$$E - T_2: \quad \ln(1 - x_A) = -\{\Delta H_b/RT\} + \beta_2 \quad (11.14)$$

where ΔH_b is the heat of fusion of B, x_A is the mole fraction of A, and β_2 is a constant applying to A in the system. However, since $x_a = 1 - x_B$ it follows that Eq. (11.14) gives:

$$E - T_2: \quad \ln(x_B) = -\{\Delta H_B/RT\} + \beta_2 \quad (11.15)$$

If x_A and x_B are known at two different temperatures, then the curve may be constructed (and the eutectic point may be calculated as the intercept between the two curves, or the root of the two equations).

ΔH may not be temperature-independent, in which case, as shown in Chap. 3, a logarithmic term has to be added.

Eutectic phase diagrams may be obtained by DSC, and one method for arriving at the diagram is the following: A finely ground mixture of A and B is produced and mixed well, and heated in the calorimeter. Reference is made to Fig. 11.13, where it is assumed that the heating causes the first thermal response (the eutectic temperature) at 40°C and the last at 120°C, the liquidus line. x_B is known from the composition, and this gives one point where the points C (liquidus temperature) and Q (eutectic temperature) can be plotted.

It is possible to carry out the trace with just one DSC determination, if it is assumed that ΔH is temperature-independent. ΔH_{total} for the entire melting is the obtained (by comparison with indium traces) from the area, A_{total} under the entire

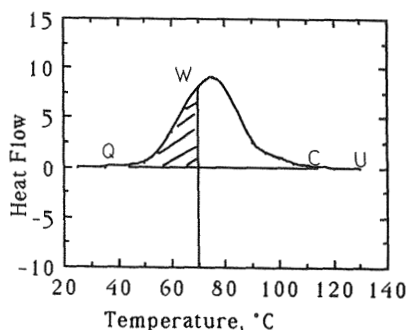


Fig. 11.13 Schematic of a DSC trace, for which the eutectic temperature is about 40°C and the liquidus line is at 120°C, at the composition in question.

trace. ΔH_W is obtained by the cross-hatched area, A_W , by comparing it with ΔH_{total} . The fraction melted f_L , is now given by:

$$f_L = A_W/A_{\text{total}} \quad (11.16)$$

f_s is $1 - f_W$, so that by use of Eq. (11.16) it is possible to calculate x_L .

The trace may, therefore, be divided into, for example, ten portions and the areas computed for each T -value, and the value of f_L for each plotted versus temperature to give the entire *liquidus* line.

There have been occasional reports in literature presenting eutectic data as *solubility* data. An example is the work by Bogdanova et al. (1998).

These authors studied melts of indomethacin and nicotinamide. Figure 11.14 shows the solubility of indomethacin as a function of its concentration in a nicotinamide–indomethacin melt. The interpretation of the data is simply that of a eutectic diagram.

Note that the *eutectic composition* is not (or only by accident) a rational fraction of moles of A and B. For a molecular compound, as mentioned in Sec. 11.4, the situation is different, and a diagram such as shown in Fig. 11.12a would lack the line segment CQ when a composition of the molar ratio is heated or cooled [i.e., would appear similar to Fig. 11.12b if only the right (or entirely the left) of the molar composition were considered].

11.10. SOLID SOLUTIONS OF THE FIRST KIND

In some systems, the solid phase crystallizing out in the areas depicting solid plus melt are not the pure compound (e.g., A on the left of the eutectic), but rather it is a solid that is a *solid solution* of B in A (or A in B on the right-hand side of the eutectic).

Figure 11.15 serves to demonstrate the definition a solid solution in the strictest thermodynamic sense. If a composition at H is allowed to cool, then at a temperature corresponding to H , solid will precipitate. This, however, will not be pure B, but rather, will contain an amount of A corresponding to the point M . If a composition of F were cooled from the melt, the solid would be B containing an amount of A corresponding to N .

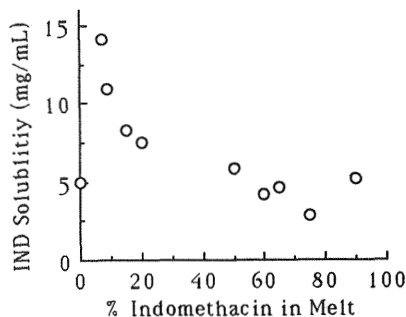


Fig. 11.14 Solubility of indomethacin as a function of its concentration in the nicotinamide–indomethacin melt. (Data from Bogdanova et al., 1998.)

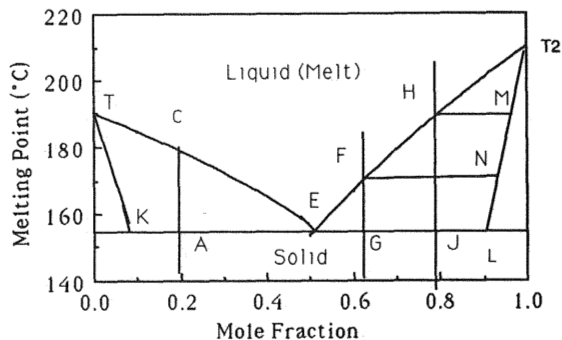


Fig. 11.15 Schematic of a situation leading to strictly solid solutions.

The situation would require equilibrium, and would take long times to establish. A and B would have to be chemically quite similar and, for instance, KCN and KSCN form solid solutions. There are inorganics that form solid solutions over the entire composition scale (e.g., Au and Ag) and, in that event, there is no eutectic at all.

In pharmaceuticals, there are no solidly documented cases of solid solutions. There were cases reported in the 1960s and 1970s (Sekiguchi and Obi, 1961; Sekiguchi et al., 1963, 1964; Goldberg et al., 1965; Guillory et al., 1969; Chiou and Niazi, 1971), but the strict criteria for solid solutions as described in the foregoing may be missing in most of these (Carstensen and Anik, 1976; Carstensen, 1981).

11.11. PARTIALLY MISCIBLE MELTS

Before continuing, a couple of words on miscibility of *liquids* is in order. Partially miscible liquids may exhibit different temperature behaviors. The most common is the situation depicted in Fig. 11.16(i). The two liquids are partially miscible between room temperature (RT) and the boiling point (Bp). If a composition of Q is created at temperature F , then the liquid mass will separate into two phases, a fraction f_F of

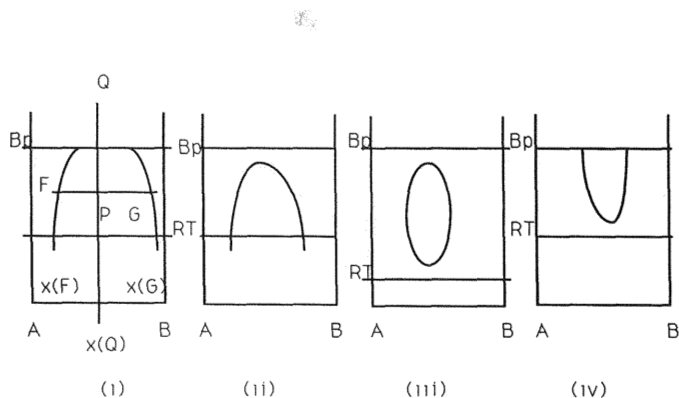


Fig. 11.16 Schematic of partial miscibility diagrams.

composition x_F , and a fraction f_G of composition x_G . The weight arm rule applies, so that

$$f_F x_F = f_G x_G = (1 - f_F x_G) \quad (11.17)$$

At times (situation in Fig. 11.16(ii)) there is complete solubility above a given temperature below the boiling point. At times (situation (iii)) there is a temperature range over which there is only partial miscibility and at times (situation (iv)), there is full miscibility at a certain temperature below the boiling point.

Melts are liquids, and miscibility of A and B may be limited. In case (i) it is necessary to heat the mixture to a temperature above the melting point of B (the higher melting constituent), and even so, there will be two phases. In cases (iii) or (iv), depending on the melting point of B, there will be a temperature range over which there is a single phase, and such systems, although they may exhibit phase separation at certain temperature, lowering the temperature will bring them into the case discussed in Secs. 11.8 and 11.9.

In cases (iii) and (iv) melting at a temperature above the melting point of B will cause a single phase, but on further heating there will be a phase separation. Both cases (i) and (ii) may lead to "separate" portions of a phase diagram, and the appearance of this may resemble that of truly solid solution discussed in Secs. 11.5 and 11.10.

11.12. THE SEPARATED PHASE: SOLID SOLUTIONS OF THE SECOND KIND

There are several possibilities for what will separate out from a molten mix as it is cooled and point C (see Fig. 11.11) is reached. There are also several possibilities for the makeup of point Q (the eutectic).

For materials that are neatly crystalline, the situation is as described in Sec. 11.2. If the composition to start with is to the left of the eutectic, *then all of B is in a very finely subdivided state.*

A situation a bit more complicated is that A crystallizes out but that, at the eutectic temperature, B remains amorphous. If this occurs, the attainment of a solid state is the point at which the rubbery amorphate phase is sufficiently viscous. The final product, then, is crystalline A dispersed in amorphous B, a *solid dispersion*. Conversely, it is obviously a solid dispersion of B in amorphous A that results.

The third case is one in which both compounds remain amorphous. Here, as has been discussed under Sec. 11.6, amorphates, the situation may be one of two cases:

1. The amorphates are mutually soluble; consequently, it is a *solid solution of the second kind* that results.
2. The amorphates are only partially miscible, accordingly, it is a second case of a solid dispersion that occurs.

11.13. MELTS

Solid dispersions were originally suggested by Chiou and Riegelman (1971) who dealt with the dispersion of drugs in a base of polyethylene glycol (PEG). This

was shown to give enhanced blood levels. It is a principle that has been successful commercially (GRISPEG).

The process of solid dispersions is carried out by (a) either comelting the drug and a meltable polymer, such as PEG, or (b) by coprecipitating the drug with the polymer from water or a solvent. Lipman and Summers (1980) and Horn and Dittert (1982), likewise have discussed the subject. The comelt process will be discussed first.

Lloyd et al. (1997) and Craig and Newton (1991) have made paracetamol (acetaminophen) and PEG 4000 solid dispersions containing 20% paracetamol by comelting in a DSC pan at 1-h storage at 70°C. On melting a single endotherm occurs at 55°C, and by cooling, recrystallization the exotherm occurs at 40°C and, contains a doublet. After reheating, a doublet occurs at 52° and 55°C. The authors suggest that the dispersions contain recrystallized polymer in both an extended stable chain form and in a metastable form, folded once.

If water is the “left” component, then the right half of the diagram constitutes the solubility/temperature curve of the “right” compound in water (Carstensen, 1977; Denbigh, 1961).

Eutectic diagrams differ if different polymorphs are used as the second component; for example, Giordano et al. (1998) employing DSC, determined eutectic diagrams of piroxicam pivalate and prioxicam and found them to be different for the two different polymorphs of piroxicam pivalate. This point is of interest because, in terms of labeling, if a label states piroxicam pivalate, x mg, then the contents of the container (e.g., tablets) should contain x mg *as pivalate*. In certain pharmaceutical situations, a salt dissociates in the solid state (e.g., if the microenvironmental pH is increased), and strictly speaking the drug substance decreases (because there is less solid present as the salt; e.g., pivalate). DSC traces may detect this type of dissociation. Strict interpretation in terms of law, would dictate that if the pivalate is the “drug,” then the free base is a “derivative drug.”

11.14. COPRECIPITATES

The solid dispersion process is carried out (a) by either comelting the drug and a meltable polymer, such as PEG; or (b) by coprecipitating the drug with the polymer from water or a solvent. Lipman and Summers (1980) and Horn and Dittert (1982), have discussed these aspects of the subject.

The question is, whether these solid dispersions are (a) solid solutions in the strictest sense, (b) finely subdivided, crystalline drug substance in a polymer matrix, or (c) amorphous drug in a polymer matrix. deVilliers et al. (1998) have described coprecipitates of acetaminophen with polyvinylpyrrolidone (PVP) formed by (a) coprecipitation, (b) recrystallization, (c) mechanical mixing, and (d) freeze-drying, and have assessed the products by X-ray diffraction and by solubility. Decrease in crystallinity was observed only in cases for which both the PVP and the acetaminophen were soluble or partly soluble (ethanol and water), and the formed amorphous phase was a glass-like, solid solution.

Bases other than PEG have been suggested over the years [e.g., Brachais et al. (1998) have suggested poly(methylglyxylate) as a base for oral, controlled drug delivery systems]. Coprecipitation yielded a better dispersion of drug in the base than comelts. The coprecipitates reported by Brachais et al. (1998) lend themselves well to compression, without slowing down the release to any extent.

The question is whether these solid dispersions are (a) solid solutions in the strictest sense, (b) finely subdivided, crystalline drug substance in a polymer matrix, or (c) amorphous drug in a polymer matrix.

11.15. COGRINDS

It is a common practice to cogrind drugs with polymers, such as HPMC (Sugimoto et al., 1998), β -cyclodextrin (Mitrevaj et al., 1996; Arias et al., 1997), chitin and chitosan (Koh et al., 1986a,b), microcrystalline cellulose (Yamamoto et al., 1974, 1976; Nakai et al., 1978), and gelatin (Kigasawa et al., 1981).

Chitosan (Portero et al., 1998) is β -(1-4)-2-amino-2-deoxy-D-glucose and is obtained by *N*-deacetylating the polysaccharide chitin. This is a substance that is abundant in nature, being the principal component of crustaceans, insects, and shells (Muzarelli, 1977). Chitosan is a good direct compression ingredient (Nagai et al., 1984; Upadrashta et al., 1992) which enhances dissolution of many compounds (e.g., nifedipine; Portero et al., 1998).

Shin et al. (1998) studied cogrinds of furosemide with crosspovidone (polyplasdone).

11.16. DISSOLUTION OF SOLID DISPERSIONS

The general purpose of solid dispersions is to improve dissolution rates. The literature is replete with examples, most of them using PEG as a dispersion vehicle. Figure 11.17 demonstrates this with a solid dispersion of ofloxacin (Okonogi et al., 1997).

Usui et al. (1998) have reported on the improvement in dissolution of ($\pm$)-4-(4-cyanoanilino)-5,6-dihydro-7-hydroxy-7H-cyclopental[d]pyrimidine) with solvent-method-produced solid dispersions using HMPC, PVP, and HPC.

The dissolution equation is given by

$$dM/dt = -kA(S - C) \quad (11.18)$$

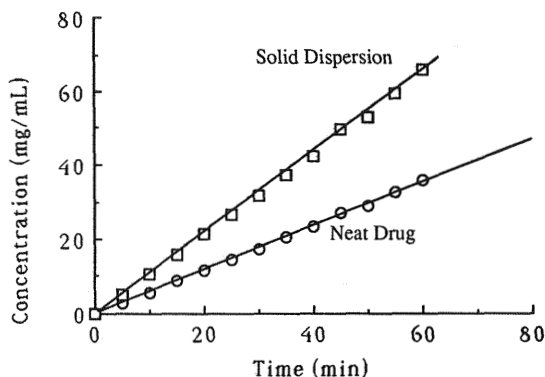


Fig. 11.17 Dissolution profiles of pure ofloxacin (circles) and in 1:4 solid dispersion in mannitol/urea made by the coprecipitation method. Dissolution of medium: distilled water, using USP paddle method at 37°C at 100 rpm from a 10 mm-diameter tablet consisting 100 mg of ofloxacin, compressed at 2 t/cm². (Data from Okonogi et al., 1997.)

where M is the amount not dissolved, k is the intrinsic dissolution rate constant, C is concentration at time t , S is solubility, and A is area.

For amorphates and (with the Ostwald Freundlich equation) also for very finely subdivided crystalline solids, the solubility S is increased over coarse crystalline material.

It is also seen from the foregoing text, that the surface area of either B or A may be greatly enhanced by forming a solid dispersion. If the drug is component B, then it is noted that for the increased surface area and, perhaps, solubility to happen, the composition must be to the left of the eutectic. This is an advantage, because it implies that the drug-loading can be considerable.

However, most successful solid dispersions have a substantial amount of PEG associated with them, and a disadvantage of the systems is actually that high-level dosage forms do not lend themselves to the approach. This is because a melt has to be produced in which B is soluble. There is often a limit on the temperature to which the melt may be heated, so that the limitation lies in producing a homogeneous melt at the higher temperature.

Increased dissolution rates, however, are also aided in that many melt-producing substances, such as PEG, complex with the drug substance, and the complexes most often have increased solubility.

Brachais et al. (1998) have suggested poly(methylglyxylate) as a base for solid dispersion. If the dissolution occurred through erosion, then the dissolution profile should be a cube-root plot, but their data do not lend themselves to this type of plotting or to square-root in time plotting. The best plotting mode as shown in Fig. 11.18 is by a loglinear decay with a slight initial burst.

SYMBOLS

A = (a) component A, (b) area

A_w = amount melted deduced from area in a DSC peak

$[A_xB_y]$ = notation for a molecular, solid compound.

B = component B

C = concentration at time t in a dissolution experiment

f = number of Gibbs' degrees of freedom

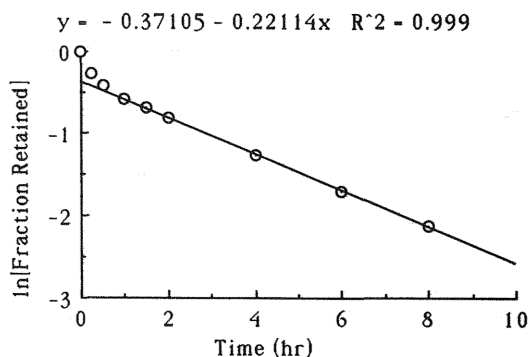


Fig. 11.18 Solid dispersion produced by coprecipitation. (Data from Brachais et al., 1998.)

$f_L = A_w/A_{\text{total}}$ = fraction melted

$f_s = 1 - f_w$ = fraction not melted

H = partial molar heat of the solid compound in ideal solution

h = enthalpy of the pure solid per mole

ΔH = heat of fusion

ΔH_A = heat of fusion of A

ΔH_b = the heat of fusion of B

ΔH_w = the cross-hatched area (fraction melted)

ΔH_{total} = heat of transition

k = intrinsic dissolution rate constant

$L = (H - h)$

M is amount not dissolved

$m_s = f_s$ = mass fraction of solid phase

$m_L = f_L$ = mass fraction of liquid phase

n = number of compounds

p = number of phases

R = the gas constant

S = solubility

T = absolute temperature

T_0 = melting point of pure compound

t = time

x_B = mole fraction of B in solid solution

x_A = mole fraction of A in solid solution B is the mole fraction of A in a mixture

x = mole fraction

x_L = mole fraction in liquidus phase

x_s = mole fraction in solidus phase

β_1 = a constant applying to B in the system

β_2 = a constant applying to A in the system

REFERENCES

- Bogdanova S, Sidzhakova D, Karaivanova V, Georgieva S (1998). *Int J Pharm* 163:1.
- Brachiais C-H, Duclos R, Vaugelade C, Huguet J, Capelle-Hue M-L, Bunel C (1998). *Int J Pharm* 169:23.
- Burger A, Ramberger R (1979). *Microchim Acta* 1979:259.
- Carstensen JT (1977). *Pharmaceutics of Solids and Solid Dosage Forms*. John Wiley & Sons, New York.
- Carstensen JT (1980). *Solid Pharmaceutics, Mechanical Properties and Rate Phenomena*. Academic Press, New York, pp 105–110.
- Carstensen JT, Anik S (1976). *J Pharm Sci* 65:158.
- Chiou WL, Niazi S (1971). *J Pharm Sci* 60:1333.
- Chiou WL, Riegelman S (1971). *J Pharm Sci* 60:1333 1281, 1376, 1569.
- Craig DQM (1990). *Drug Dev Ind Pharm* 16:250.
- Craig DQM, Newton JM (1991). *Int J Pharm* 76: 17.
- Denbigh K (1961). *The Principles of Chemical Equilibrium*. Cambridge University Press, pp 256–264.
- DeVilliers MM, Wurster DE, Van der Watt JG, Ketkar A (1998). *Int J Pharm* 163:219.
- Ford JL (1986). *Pharm Acta Helv* 61:69.

- Franks F (1990). *Cryo Lett* 11:93.
- Frazer JCW (1931). In: Taylor HS ed, *Treatise on Physical Chemistry*. Van Norstrand, New York, p. 356, 556.
- Garner WE (1955). *Chemistry of the Solid State*. Butterworths Scientific, London, pp 213–216.
- Giordano F, Gazzaniga A, Moyano JR, Ventura P, Zanol M, Pever T, Carima L (1998). *J Pharm Sci* 87:333.
- Goldberg AH, Gibaldi M, Kanig JL (1965). *J Pharm Sci* 54:1145.
- Guillory JK, Huang S, Lach J (1969). *J Pharm Sci* 58:301.
- Hildebrand GE, Müller–Goymann CC (1997). *J Pharm Sci* 86:854.
- Himes VL, Mighell AD, DeCamp WH (1981). *Acta Crystallogr B* 37:2242.
- Horn D, Dittert W (1982). *J Pharm Sci* 71:1021.
- Levine H, Slade L (1988). *Cryo Lett* 9:21.
- Lippman EC, Summers MP (1980). *J Pharm Pharmacol* 32:21P.
- Lloyd GR, Graig DQM, and Smith A (1997). *J Pharm Sci* 86:991.
- Lowes MMJ, Cairfa MR, Lötter AP, Van Der Watt JG (1987). *J Pharm Sci* 76:744.
- MacKenzie AP (1977). *Dev Biol Stand* 36:51.
- Muzarelli RAA (1977). *Chitin*, Pergamon, Oxford.
- Nagai T, Sawayanagi Y, Nambu N (1984). *Chitin, Chitosan and Related Enzymes*, Academic Press, Orlando, FL, pp 21–39.
- Okonogi S, Oguchi T, Yonemochi E, Puttipipatkachorn S, Yamamoto K (1997). *Int J Pharm* 156:175.
- Pohlman H, Gulde C, Jahn R, Pfeiffer S (1975). *Pharmazie*, 30, H11:709.
- Portero A, Remunán–Lopez C, Vila–Jato JL (1998). *Int J Pharm* 175:75.
- Reboul JP, Cristau B, Soyfer J–C, Astier J–P (1981). *Acta Crystallogr B* 37:1844.
- Reck G, Dietz G (1986). *Cryst Res Technol* 21:1463.
- Sekiguchi K, Obi N (1961). *Chem Pharm Bull*, 9:866.
- Sekiguchi K, Obi N, Ueda Y, Nakamori Y (1963). *Chem Pharm Bull*, 11:1108, 1123.
- Sekiguchi K, Obi N, Ueda Y (1964). *Chem Pharm Bull*, 12:134, 164.
- Shin S–C, Oh I–J, Lee Y–B, Choi H–K, Choi J–S (1998). *Int J Pharm* 175:17.
- Suzuki T, Franks, F (1993). *J Chem Soc Faraday Trans*, 89:3283.
- Terrence, CF, Sax M, Fromm GH, Chang C–H, Yoo C (1983). *Pharmacology*, 27:85.
- Turel I, Bukovec P, Quirós M (1997). *Int J Pharm* 152:59.
- Upadrashta SM, Katikaneni PR, Nuessle NO (1992). *Drug Dev Ind Pharm* 18:1701.
- Usui F, Maeda K, Kusai A, Ikeda M, Nishimura K, Yamamoto K (1998). *Int J Pharm* 170:247.
- Yu L (1995). *J Pharm Sci* 84:966.

This Page Intentionally Left Blank

12

Dissolution from Particles and Surfaces

12.1. The Noyes–Whitney Equation	191
12.2. The Wood’s Apparatus: Sink Plate Dissolution	192
12.3. Dissolution by Calorimetry	194
12.4. Nonsink, Constant Surface Area Dissolution	194
12.5. Effect of Variables	194
12.6. Film Theory and the Levich Equation	195
12.7. The Nelson and Shah Equation	197
12.8. The Hixson–Crowell (Cube Root) Equation	198
12.9. Constancy of the Shape Factor	202
12.10. Time Dependence of the Shape Factor During Dissolution	203
Symbols	206
References	208

The rate with which a drug substance dissolves either from neat drug or from a dosage form is of great importance because it often governs the biopharmaceutical profiles of the drug.

12.1. THE NOYES–WHITNEY EQUATION

The equation developed by Noyes and Whitney in 1887, states that (Fig. 12.1), when a substance (with solubility S) dissolves from a planar surface of surface A , then its dissolution rate, $-dm/dt$ (where m is mass and t is time), is given by

$$-dm/dt = kA(S - C) \quad (12.1)$$

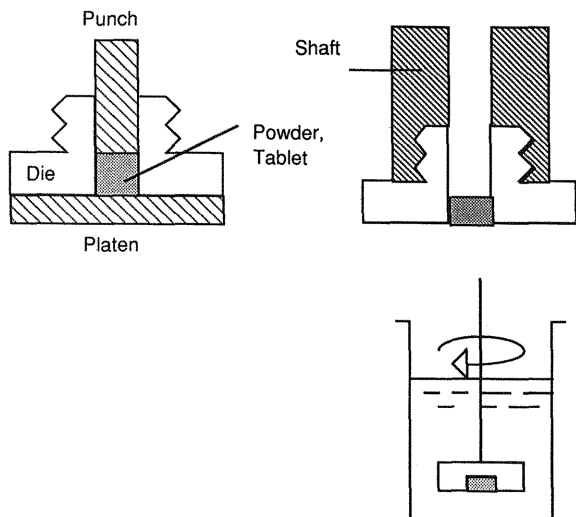


Fig. 12.1 Wood's apparatus.

where k is the intrinsic dissolution rate constant (cm/s), and C is the concentration at time t . If the dissolution takes place into a volume of dissolution liquid V , then the concentration will change with time by a modification of Eq. (12.1)

$$dm/dt = VdC/dt = -kA(S - C) \quad (12.2)$$

12.2. THE WOOD'S APPARATUS: SINK PLATE DISSOLUTION

Many criticisms have been voiced against Eq. (12.2), but in general it is correct, and it will be assumed to be so in the following. Experimentation can be carried out with constant surface as when using a Wood's apparatus as shown in Fig. 12.1. In this, a die (as shown in the upper left of the figure), is placed on a platen and filled with powder. The powder is then compressed. The die is removed, and a shaft screwed on to it (as shown in the upper right of the figure). This is then lowered into a dissolution container, the shaft is attached to a motor, and the die is rotated, most often at 50 rpm.

With smaller amounts of drug available it suffices to make a small pellet and encasing it in wax and exposing only one face to a dissolution medium. Alternatively a fairly constant surface area can be assured by simply employing a large excess of powder so that only a small amount of the solid, in the long run, dissolves. In all of these cases Eq. (12.2) may be integrated to give

$$\ln[1 - (C/S)] = -(kA/V)t \quad (12.3)$$

or

$$C = S[1 - \exp(-\{kA/V\}t)] \quad (12.4)$$

A typical curve following Eq. (12.4) is shown in Fig. 12.2.

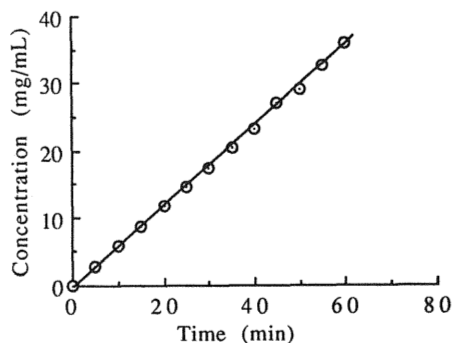


Fig. 12.2 Dissolution of pure ciprofloxacin in distilled water, using *USP* paddle method at 37°C at 100 rpm from a 10-mm-diameter tablet containing 100 mg of OFX compressed at 2 t/cm². (Data from Okonogi et al., 1997.)

The use of a compressed disk is referred to as a Wood's apparatus (Wood et al., 1963) when the setup is as shown in the second drawing in Fig. 12.1. In this manner it is felt that the area will stay constant (see Fig. 12.2).

Plate dissolution is at best an estimate, and probably a fairly inaccurate estimate, of dissolution. The general idea is that the surface that is exposed to the liquid (Fig. 12.3A) will stay constant during the dissolution and simply recede (see Fig. 12.3B). However, it is more likely that it will become uneven during dissolution (Carstensen, 1974, 1977) (see Fig. 12.3C). The other problem is that often too little compression pressure is applied to prevent the compact from being porous. This, essentially, should cause curvature in the dissolution plotted according to Eq. (12.4). Often as little as 1-ton/cm² pressure is applied, and only for substances with very low elastic yield value, will this suffice to make a nonporous compact.

Nevertheless the method is useful, because it provides some measure of comparison (e.g., between the k -values for different salts of a drug substance). But even under such condition direct comparison is not exacting because the substances may have different yield values; hence, they give different porosities.

The best method is to repeat an experiment several times using different compression pressures until a consistent value of k is obtained. Low pressures lead to wrong k -values and erroneous conclusions (Chen and Grant, 1998; Grant et al., 1984).

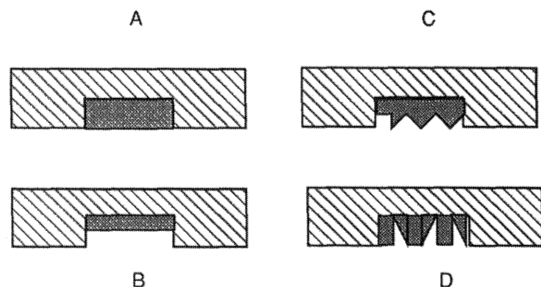


Fig. 12.3 Types of compact formations in plate dissolution.

One reason that low pressures are preferred by many investigators is that higher pressures may lead to polymorphic transformations. *It is always advisable to remove a small amount of solid from the back of the compact and test it for morphology* (Guillory, 1992).

In the critical time path for product development, solid-dosage forms (tablets or capsules) must eventually be manufactured for the clinic (e.g., in clinical phase II). If possible, the drug substance per se is subjected to a dissolution test in a Wood's apparatus (Wood et al., 1963). This test is useful, although quite dependent on hydrodynamic conditions, as shall be discussed shortly. It is possible from data of the foregoing type to calculate k (cm/s).

The general concern with dissolution is that of bioavailability. It has been suggested (Riegelman, 1979) that if k is obtained under sink conditions over a pH range of 1–8 at 37°C in a USP vessel by way of Eq. (12.3) at 50 rpm, then if the dissolution rate constant (kA/V) is greater than $1 \text{ mg min}^{-1} \text{ cm}^{-2}$, then the drug is not prone to give dissolution-rate-limited absorption problems. On the other hand, if the value is less than 0.1, such problems can definitely be anticipated, and compounds with values of kA/V of from 0.1 to $1 \text{ mg min}^{-1} \text{ cm}^{-2}$ are in a gray area. For compound selectivity it is frequently useful to express dissolution findings in terms of k (i.e., in cm/s).

12.3. DISSOLUTION BY CALORIMETRY

For a small amount of powder, dissolution of the particulate material can often be assessed (and compared with that of other compounds), by placing the powder in a calorimeter (Iba et al., 1991) and measuring the heat evolved as a function of time. The surface area must be assessed microscopically (or by image analyzer), and the data must be plotted by a cube-root equation. (Hixson and Crowell, 1931), a point to be discussed presently.

$$1 - [M/M_0]^{1/3} = -(2kS/\rho r)t \quad (12.5)$$

where M is mass not dissolved, M_0 the initial amount subjected to dissolution, ρ is true density, S is solubility, and r is the mean "radius" of the particle. The method is simply comparative, not absolute, owing to the hydrodynamics being different in the calorimeter than it would be in a dissolution apparatus. M/M_0 is here proportional to the area under the (differential) calorimetric curve at time t , divided by the total area under the calorimetric curve.

12.4. NONSINK, CONSTANT SURFACE AREA DISSOLUTION

If constant surface area dissolution is carried beyond the sink level, then curvature results. Figure 12.4 demonstrates this (Usui et al., 1998). It is noted that initially (up to 10 min) the curve is fairly straight, but then begins to curve. If plotted logarithmically, it linearizes (Fig. 12.5).

12.5. EFFECT OF VARIABLES

The variables in Eq. (12.1) are the solubility, the surface area, and the dissolution rate constant. Although k is thought of as a constant, it is only a constant at a given

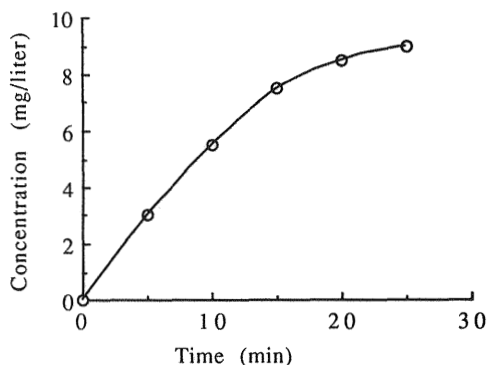


Fig. 12.4 Dissolution of $(\pm)$ 4-(4-cyanoanilino-5,6-dihydro-7-hydroxy-7*H*-cyclopental[*d*]pyrimidine) hydrochloride. (Data from Usui et al., 1998.)

temperature and under given hydrodynamic conditions. Its hydrodynamic variability will be discussed in a subsequent section.

Relative to surface area, Carstensen (1977) has pointed out that as the surface (see Fig. 12.1) recedes, the area may not be “smooth,” and the cross section of the die, assumed to be the surface area, may not be so. There is also the problem with adhered “dust,” which may give an initial burst. The powder used, should be fine, for otherwise, particles can “fall out.”

One hidden variable, rarely discussed, is the pressure at which the compact is made. To carry out the experiment in a duplicable fashion, several curves should be generated using different compression pressures. The pressure at which the curves become duplicable is then the pressure that should be indicated. Authors most often indicate the pressure used, but do not justify the choice.

12.6. FILM THEORY AND THE LEVICH EQUATION

Equation (12.1) was, for a while, explained in the following fashion: reference is made to Fig. 12.6. A plane surface allows dissolution of the solid into solution. It

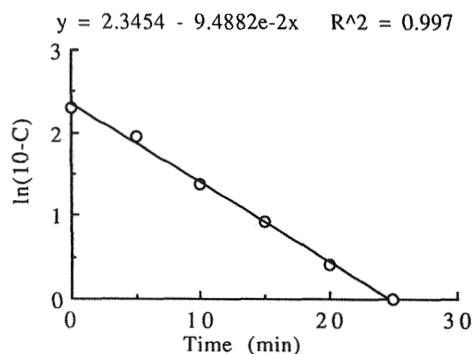


Fig. 12.5 Data in Fig. 12.4 treated according to Eq. (12.3) assuming a solubility of $10 \mu\text{g/mL}$.

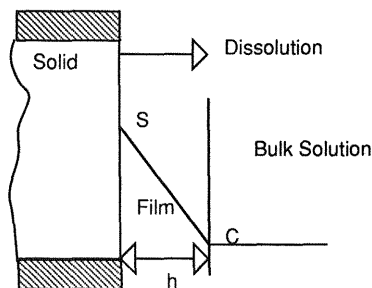


Fig. 12.6 Schematic of film model.

is assumed that there is a film, of thickness h , which is attached to this, and that the layer adjacent to the surface is saturated, whereas at distance h , the concentration is that of the bulk solution (i.e., C).

Fick's law now gives:

$$J = -D(dC/dy) \quad (12.6)$$

where D is the diffusion coefficient, y is distance perpendicular to the plate, and J is the flux. This latter is $(1/A) dM/dt$, so that Eq. (12.14) becomes:

$$(1/A)dM/dt = -D(dC/dy) \quad (12.7)$$

It is noted that the amount dissolved M equals the volume V of the dissolution medium times the concentration. Therefore, if it is assumed that D is distance-independent, then

$$dC/dy = (C - S)/h \quad (12.8)$$

so that (Eq. 12.7) becomes

$$dM/dt = -VdC/dt = (D/h)A(S - C) \quad (12.9)$$

hence,

$$dC/dt = (D/h)(A/V)(S - C) \quad (12.10)$$

that is, the intrinsic dissolution rate constant from Eq. (12.2) becomes

$$k = D/h \quad (12.11)$$

Equation (12.2) is often written in the fashion of Eq. (12.10).

The Stokes-Einstein equation states that

$$D = \kappa T / (6\pi\eta a) \quad (12.12)$$

where κ is the Boltzmann constant, T is absolute temperature, η is viscosity of the dissolution medium, and a is the molecular "radius." This inserted in Eq. (12.19) gives

$$k = \kappa T / (6h\pi\eta a) \quad (12.13)$$

or

$$\ln(k/T) = -\ln[\eta] + \ln[\kappa/(6\pi a)] \quad (12.14)$$

Carstensen and Patel (1975) studied the dissolution of oxalic acid at different temperatures and reasoned that $\ln[k/T]$ should have the temperature dependence of the viscosity: that is,

$$\ln[\eta] = (E/RT) + \beta \quad (12.15)$$

where β is a constant. It is noted that viscosity decreases with increasing temperature so that for viscosity the activation energy, E_a , is negative. They found that the slope of the modified Arrhenius plot [see Eq. (12.14)] was very close to the activation energy for water's viscosity.

In spite of this evidence, there is good reason to believe that it is the Levich equation, rather than the film theory as explained here, that applies to plate dissolution. The Levich equation states that

$$\text{Rate} = QAD^{2/3} \nu^{1/6} \omega^{1/2} \quad (12.16)$$

where Q is a constant, ν is kinematic viscosity, and ω is rotational speed of the plate.

It is noted that by conducting the experiment at different rotational speeds it is possible, by plotting the dissolution rate versus the square root of ω to obtain the diffusion coefficient.

12.7. THE NELSON AND SHAH EQUATION

In a stream passing over a plate, the dissolution is dictated by the Ficksian equation

$$D\partial^2 C/\partial y^2 - V_x(y)\partial C/\partial x = 0 \quad (12.17)$$

Here (as denoted in Fig. 12.7), D is diffusion coefficient, C is concentration, y is distance from and perpendicular to the plate, x is distance along the x -axis, V_x is velocity in the x direction (the dependence on y -value is denoted $V_x(y)$), and C is concentration. The first term is diffusional and the second one is convective. Assuming, as is shown in the left profile in Fig. 12.7 that the velocity increases linearly with distance from the plate, then

$$V_x(y) = \beta y \quad (12.18)$$

$V_x(y)$ is a linear velocity that may be converted to mass flow rate ($Q \text{ cm}^3/\text{s}$) by multiplying it by the cross section of the channel.

The initial and boundary conditions are

$$\begin{aligned} C_0 = 0; x = 0' \quad 0 \leq y < \infty \\ C_l = S; y = 0, 0 < x < L \quad C_l = 0; y = \infty \end{aligned} \quad (12.19)$$

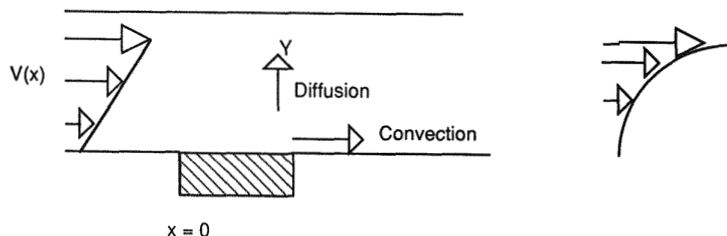


Fig. 12.7 Schematic of dissolution from a plate by a stream.

Rao et al. (1997) concluded that the dissolution from a Shah–Nelson plate (Shah and Nelson, 1975) of griseofulvin into a surfactant solution should exhibit the following flux, J

$$J = 0.808D_q^{2/3}S_m[6v/H^2B]^{1/3}bL^{2/3} \tag{12.20}$$

where D_q is a composite diffusion coefficient, S_m is the solubility of griseofulvin in the micellar solution, v denotes the rate of flow, B and H are the width and height of the channel and L and b are the length and width of the compress. A similar equation, without the m -subscript, will hold with the foregoing boundary and initial conditions, for diffusion into a simple solution.

According to this the log of R should be linear in the log of Q with a slope of $1/3$, and indeed they find such a relation.

It is seen from Fig. 12.8 that the relation is linear, but that the position of the line is not identical with the theoretical line.

One problem with the experiments is the assumption of linearity of $V_x(y)$, and the relation is probably more parabolic as shown in the right-hand profile in Fig. 12.7.

12.8. THE HIXSON–CROWELL (CUBE ROOT) EQUATION

The foregoing text has concentrated on the basic mechanisms for dissolution from the particle surface into a moving body of water. For dosage forms, the drug substance is usually present as a multiparticulate population. If the particles are all the same size then the population is *monodisperse*. If not, then it is denoted *polydisperse*. The first topic at this point will be the dissolution of a monodisperse powder under sink conditions.

The dissolution of a *particle* and a *monodisperse particle populations* were first derived by Hixson and Crowell (1931). They assumed the particles to be spherical, and their derivation, in modified form, will be presented here, with the exception that

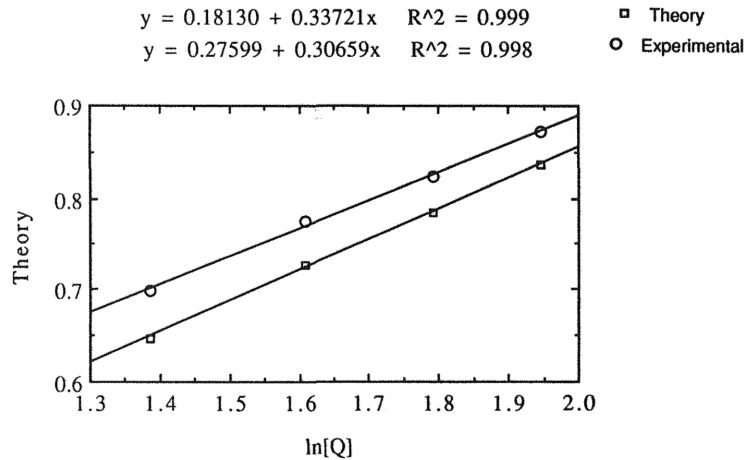


Fig. 12.8 Dissolution of griseofulvin into solutions of sodium dodecyl sulfate (20 mM) solution. (Data from Rao et al., 1997.)

a cubical particle shape will be assumed, and the equation will be derived for a single particle of sidelength b .

If we assume the particle to be *isotropic* and dissolving under sink conditions, then the Noyes–Whitney equation becomes:

$$dm/dt = -ksS \quad (12.21)$$

lowercase s denotes the surface of the particle. From the geometry it follows that

$$m = \rho b^3 \quad (12.22)$$

and

$$s = 6b^2 \quad (12.23)$$

so that Eq. (12.21) becomes

$$3\rho b^2 db/dt = -6kb^2 S \quad (12.24)$$

or

$$db/dt = -2kS/\rho \quad (12.25)$$

This, after initial conditions, integrates to

$$b = b_0 - (2kS/\rho)t \quad (12.26)$$

or

$$b_0 - b = Kt \quad (12.27)$$

where the cube-root dissolution rate constant K is given by

$$K = (2kS/\rho)t \quad (12.28)$$

It is noted that

$$b/b_0 = \{v/v_0\}^{1/3} = \{m/m_0\}^{1/3} \quad (12.29)$$

so that Eq. (12.26) may be rewritten:

$$1 - (m/m_0)^{1/3} = K't \quad (12.30)$$

where

$$K' = 2kS/(\rho b_0) \quad (12.31)$$

The rate constants K and K' are referred to as the *particle cube-root rate constants*.

Shape factors have been dealt with before, but to repeat, the surface shape factor, α_s , is defined by the equation

$$s = \alpha_s d^2 \quad (12.32)$$

where s is the surface of the particle, and d is its “size” (i.e., a defined dimension), such as the width of the particle, b . Similarly the volume v of the particle is given by (Dallavalle, 1948) as

$$v = \alpha_v d^3 \quad (12.33)$$

The *overall* shape factor Γ is given by the equation

Table 12.1 Γ -Values for Some Isometric Shapes

Shape	Shape factor	Numerical value
Sphere	$[6]^{2/3}\pi^{-1/3}$	4.834
Cube	6	6
Isometric cylinder ^a	$1.5 [4]^{2/3}\pi^{-1/3}$	5.54

^aA cylinder for which the diameter equals the height.

$$\Gamma = s/(v^{2/3})$$

(12.34)

so that, by combining these three equations it follows that

$$\Gamma = \alpha_s/(\alpha_v^{2/3})$$

(12.35)

The overall shape factor will be referred to as the *particle shape factor* in the text immediately following. Particle shapes for which the shape factor is independent of size are denoted *isometric*, and examples of this are listed in Table 12.1 with the appropriate Γ -values. The shape factor for a sphere is smaller than that for any other particle shape.

In the following there will be two situations that will be considered: (a) the dissolution of a monodisperse powder (Fig. 12.9), and it is noted here that all the particles disappear at the same time. (b) The other situation is for *one* particle. The Noyes–Whitney equation dictates that for N particles

$$dm/dt = -kNsS$$

(12.36)

If N particles, each of mass m , volume v , and density ρ are allowed to dissolve, then the mass m of a particle is the density ρ times the volume v and it follows that Eq. (12.36) for N particles is

$$(N\rho)dv/dt = NksS$$

(12.37)

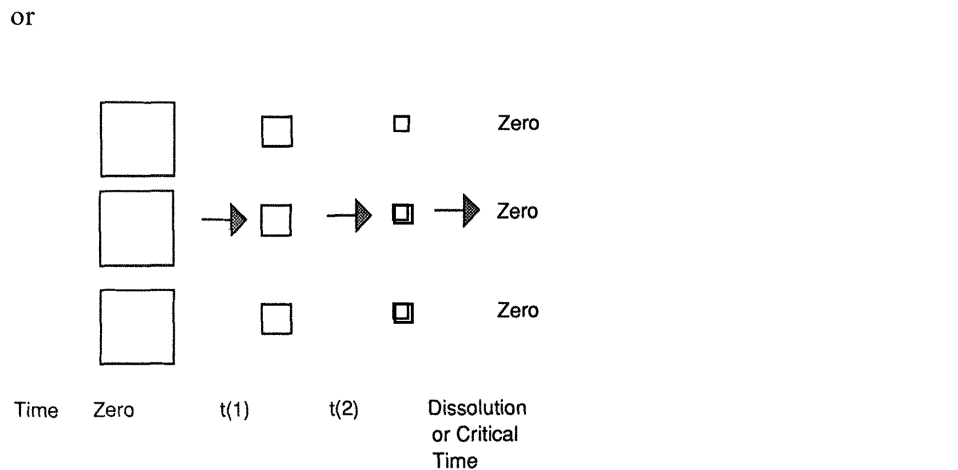


Fig. 12.9 The situation during dissolution of a monodisperse powder. Note that all the particles disappear at the same time.

$$dv/dt = k\Gamma v^{2/3}S/\rho \quad (12.38)$$

Because $s = \Gamma v^{2/3}$, therefore

$$dv/[v^{2/3}] = (k\Gamma S/\rho)dt \quad (12.39)$$

This integrates (after initial conditions are imposed) to

$$v_0^{1/3} - v^{1/3} = (k\Gamma S/3\rho)t = K_v t \quad (12.40)$$

where K_v is the cube-root dissolution rate constant based on volume for one particle.

$$1 - [v/v_0]^{1/3} = \{(k\Gamma S)/(\rho 3v_0^{1/3})\}t \quad (12.41)$$

It is noted that

$$v/v_0 = N\rho v/N\rho v_0 = M/M_0 \quad (12.42)$$

where M is the total mass of the undissolved powder at time t , and M_0 is the amount before dissolution. Hence, the more familiar form of Eq. (12.40) emerges.

$$1 - [M/M_0]^{1/3} = \{(k\Gamma S)/(\rho 3v_0^{1/3})\}t \quad (12.43)$$

Since

$$v_0^{1/3} = (m_0/\rho)^{1/3} = \{M_0/(N\rho)\}^{1/3} \quad (12.44)$$

Equation (12.43) may be rewritten

$$\begin{aligned} 1 - [M/M_0]^{1/3} &= \{(k\Gamma S)/(\rho 3(M_0/N\rho)^{1/3})\}t \\ &= \{(k\Gamma S)\rho^{-2/3}M_0^{-1/3}N^{1/3}/3\}t = K'_{mn}t \end{aligned} \quad (12.45)$$

where

$$K'_{mn} = (k\Gamma S)\rho^{-2/3}M_0^{-1/3}N^{1/3}/3 \quad (12.46)$$

is the *relative rate constant based on a population of N particles*.

Inserting Eq. (12.44) in Eq. (12.40) gives

$$[M_0/(N\rho)]^{1/3} - [M/(N\rho)]^{1/3} = (k\Gamma S/3\rho)t \quad (12.47)$$

or

$$M_0^{1/3} - M^{1/3} = [(N\rho)]^{1/3}(k\Gamma S/3\rho)t = K_{mn}t \quad (12.48)$$

where

$$K_{mn} = N^{1/3}k\Gamma S\rho^{-2/3}/3 \quad (12.49)$$

K_{mn} is the *cube-root constant of N particles based on mass*. The various rate constants are summarized in the symbol list at the end of the chapter. It is important to keep an account of which dissolution rate constant is being discussed, because incorrect conclusions may be drawn from employing an incorrect definition.

It is worth repeating that cube-root dissolution *in the strictest sense* is derived from the following assumptions:

1. The particles are isometric.

2. The population is monodisperse.
3. The dissolution is isotropic.
4. Sink conditions prevail.

However, the first assumption may be studied separately. It is important to investigate whether the cube-root equation also holds for situations in which the particle is not isometric.

12.9. CONSTANCY OF THE SHAPE FACTOR

In the Hixson–Crowell equation, it is assumed that the shape-factor is constant during the dissolution event (i.e., an isometric particle will dissolve according to this equation).

It is, however, not only the effect of the shape factor that is of importance. The intrinsic dissolution rate constant k is assumed to be a constant for the substance.

Much dissolution work has been done with this assumption, in spite of the thorough work of Pedersen and Brown (1976), who studied the dissolution from various faces of crystals of different morphology, and derived equations that describe their dissolution behavior. The interest in this lies in (a) whether there are situations for which the shape factor stays constant, and (b) if it does not, to study the shape factor as a function of dissolution time. The former will be addressed first and after that a derivation will be presented to study the *extent* to which changes in shape factor may affect the cube-root law. The initial steps of the derivations follow fairly closely those of Pedersen and Brown (1975, 1976), and that the shape factor calculations are the ones unique to our theme developed thereafter.

There is one (probably very common) situation that allows the Hixson–Crowell equation to be used without adjustment for change in shape factor during the dissolution. It is often postulated that dissolution rate constants (k ; cm/s) are numerically identical, but opposite in sign to crystallization rate constants.

If a crystal grows from a nucleus in the b , h , and L -directions (Fig. 12.10) with constants k_b , k_h , and k_l , given by

$$k_h = (h/b)k_b \quad \text{or} \quad k_h/h = k_b/b \quad (12.50)$$

$$k_l = (L/b)k_b \quad \text{or} \quad k_l/L = k_b/b \quad (12.51)$$

then, if these constants are also dissolution rate constants, then a parallelepiped with sides b , h and l will dissolve by the equations

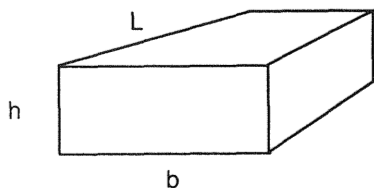


Fig. 12.10 Schematic of ideal crystal.

$$b = b_0 - k_b t = b_0 \{1 - (k_b/b_0)t\} \quad (12.52)$$

$$h = h_0 - k_h t = h_0 \{1 - (k_h/h_0)t\} = h_0 \{1 - (k_b/b_0)t\} \quad (12.53)$$

$$L = L_0 - k_b t = L_0 \{1 - (k_L/L_0)t\} = L_0 \{1 - (k_b/b_0)t\} \quad (12.54)$$

The surface area s and the volume v are given by

$$\begin{aligned} s &= 2b_0 \{1 - (k_b/b_0)t\} h_0 \{1 - (k_b/b_0)t\} + 2L_0 \{1 - (k_b/b_0)t\} h_0 \{1 - (k_b/b_0)t\} \\ &\quad + 2L_0 \{1 - (k_b/b_0)t\} h_0 \{1 - (k_b/b_0)t\} = 8(L_0 + h_0 + b_0) \{1 - (k_b/b_0)t\}^2 \end{aligned} \quad (12.55)$$

$$v = L_0 \{1 - (k_b/b_0)t\} h_0 \{1 - (k_b/b_0)t\} b_0 \{1 - (k_b/b_0)t\} \quad (12.56)$$

so

$$v^{2/3} = \{L_0 b_0 h_0\}^{2/3} \{1 - (k_b/b_0)t\}^2 \quad (12.57)$$

That is, the shape factor

$$s/v^{2/3} = 8(L_0 + h_0 + b_0)/\{[L_0 b_0 h_0]^{2/3}\} \quad (12.58)$$

This is independent of time; hence, the shape factor, under these conditions, will stay constant during the dissolution event.

12.10. TIME DEPENDENCE OF THE SHAPE FACTOR DURING DISSOLUTION

It is for the reasons stated in Sec. 12.9 that most often the Hixson–Crowell equation works well. At times, the shape factor changes sufficiently during a dissolution run that there are deviations from the cube root law. The extent to which this happens will be discussed in the following.

It has been shown that for a single isometric particle [see Eq. (12.31) multiplied through by ρ]

$$\rho dv/dt = k\Gamma v^{2/3} S \quad (12.59)$$

Since $m = \rho v$ it follows that

$$\begin{aligned} dm/dt &= k\Gamma S(m/\rho)^{2/3} \\ dm/m^{2/3} &= -K\Gamma S\rho^{-2/3} \end{aligned} \quad (12.60)$$

Lai and Carstensen (1978) studied the effect for isotropically dissolving oxalic acid cylinders to establish the effect of the shape factor on the dissolution pattern. Nonisotropic shapes were simulated by cylinders, and the effect of dissolution on the theoretical shape factor determined. This was then compared with the actual dissolution of a cylinder and good agreement was observed. It is only when a particle is isometric (i.e., when Γ is independent of dimension) that this may be expected.

Lu et al. (1993) used the concept proposed by Lai and Carstensen (1978) of imitating the shape of a crystal by a cylinder, and found that this model yields a better fit of dissolution data for hydrocortisone particles than a similar model using spheres as a model.

Lu et al. (1993) assume the shape factor to be constant during the dissolution event, a fact that is not correct and the ramifications of this will be discussed in the following.

Consider a parallelepiped of length L breadth b , and height h as shown in Fig. 12.10. The area s and volume v of a *particle* with such a geometry are given by the following equations.

$$s = 2(Lb + hL + bh) \quad (12.61)$$

$$v = Lbh \quad (12.62)$$

The Noyes–Whitney equation under sink conditions states that

$$dm/dt = \rho dv/dt = -ksS \quad (12.63)$$

Combining Eqs. (12.61), (12.62), and (12.63) now gives

$$\rho dv/dt = 2kS(Lb + hL + bh) \quad (12.64)$$

Since v is a composite function of L , b , and h , the rate of change of volume relative to time can be written as

$$\begin{aligned} dv/dt &= \{dv/dL\}\{dL/dt\} + \{dv/dt\}\{db/dt\} + \{dv/dh\}\{dh/dt\} \\ &= bh(dL/dt) + Lh(db/dt) + Lb(dh/dt) \end{aligned} \quad (12.65)$$

This is introduced into Eq. (12.63) to give

$$bh\{dL/dt\} + Lh\{db/dt\} + lb\{dh/dt\} = -\{2kS/\rho\}(Lb + hL + bh) \quad (12.66)$$

or

$$\begin{aligned} (1/L)\{dL/dt\} + (1/b)\{db/dt\} + (1/h)\{dh/dt\} \\ = (-2ks/r)\{(1/L) + (1/b) + (1/h)\} \\ = -K\{(1/L) + (1/b) + (1/h)\} \end{aligned} \quad (12.67)$$

This differential equation is in the separate variable form. Hence, it follows that

$$dL/dt = db/dt = dh/dt = -K \quad (12.68)$$

where

$$K = 2kS/\rho \quad (12.69)$$

This implies isotropic dissolution. These expressions can be integrated to obtain relations between the crystal dimensions and time of dissolution. If l_0 , b_0 , and h_0 are the initial length, breadth, and height of the crystal, then integration of Eq. 12.68 gives

$$L = L_0 - Kt = L_0\{1 - (K/L_0)t\} \quad (12.70)$$

$$h = h_0 - Kt = h_0\{1 - (K/h_0)t\} \quad (12.71)$$

$$b = b_0 - Kt = b_0\{1 - (K/b_0)t\} \quad (12.72)$$

Denoting:

$$1 - (h/h_0) = 1 - (b/b_0) = (1 - L/L_0) = u \quad (12.73)$$

where u is dimensionless, it follows that

$$u = Kt/h_0 = Kt/b_0 = Kt/L_0 \quad (12.74)$$

Employing these *identities* Eqs. (12.78 to 12.80) become:

$$L = L_0 - uh_0 \quad (12.75)$$

$$h = h_0 - uh_0 \quad (12.76)$$

$$b = b_0 - uh_0 \quad (12.77)$$

It should be noted that just before dissolution starts $h = h_0$ and, at the point when the crystal completely dissolves, $h = 0$. Hence, the domain of u is $[0,1]$. The following equations ensue by inserting Eq. (12.69) into Eq. (12.74)

$$u = \{2kS/(\rho h_0)\}t \quad (12.78)$$

To determine u , we consider the fraction of amount undissolved ($F = m/m_0$). F can be expressed as the ratio of instantaneous volume of the dissolving particle to its initial volume, density being constant, that is,

$$\begin{aligned} F &= Lbh/(L_0b_0h_0) = (L_0 - uh_0)(b_0 - uh_0)(h_0 - uh_0)/(L_0b_0h_0) \\ &= \{1 - (u/L_0)h_0\}\{1 - (u/b_0)h_0\}\{1 - (u/h_0)\} \end{aligned} \quad (12.79)$$

Two shape ratios are now defined in the following fashion which are indicative of the shape of the crystal, namely,

$$p = L_0/h_0 \quad (12.80)$$

$$q = b_0/h_0 \quad (12.81)$$

Rearranging the foregoing equation using these two ratios gives the following result

$$F = \{1 - u\}\{1 - (u/q)\}\{1 - u/p\} \quad (12.82)$$

This is a third-degree equation in u . The criteria for choosing the "correct" root of the possible three is that it should be a real number between 0 and 1. F can be obtained from dissolution data, which enables one to solve Eq. (12.82) for u . From Eq. (12.78), it is clear that a linear relation between u and t exists. Adequate linearity for a plot of u versus t has been demonstrated by Lai and Carstensen (1978) for cylindrical tablets of oxalic acid.

The slope of such a plot gives the value of the intrinsic dissolution rate constant if the solubility, density, and initial dimensions of the dissolving particle are known.

Isotropicity and isometricity are some of the basic assumptions in the derivation of the Hixson-Crowell cube-root law. A cube, a sphere, and a right circular cylinder are examples of isometric geometries because their shape factors are independent of their dimensions. Real particles are far from being isometric. The shape factor for one particle is defined as

$$\Gamma = sv^{-2/3} \quad (12.83)$$

so for the parallelepiped model described in the foregoing

$$\Gamma = 2(Lb + bh + Lh)(lbh)^{-2/3} \quad (12.84)$$

Inserting Eqs. (12.83), (12.84), and (12.85) into Eq. (12.92) yields

$$\Gamma = \frac{2\{(L_s - uh_0)(b_0 - uh_0) + (b_0 - uh_0)(h_0 - uh_0) + (L_0 - h_0)(h_0 - uh_0)\}}{(L_0 - uh_0)(b_0 - uh_0)(h_0 - uh_0)} \quad (12.85)$$

Rearranging this equation to write it in terms of the shape ratios p and q , gives

$$\Gamma/2 = \frac{\{(q-u)(q/p) - u\}^{1/3}}{(1-u)^{2/3}} + \frac{\{(1-u)(q/p) - u\}^{1/3}}{(q-u)^{2/3}} + \frac{\{(q-u)(q/p) - u\}^{1/3}}{(q/p-u)^{2/3}} \quad (12.86)$$

By way of this expression it is possible to calculate the shape factor for the paralleliped geometry considered here, as a function of reduced time. Lai and Carstensen (1978) followed a similar approach for cylindrical tablets with different radius/height ratios. They found that, expectedly, for an isometric tablet (ratio = 1) there was no change in the shape factor as the dissolution proceeded. However, significant changes in the shape factor were encountered as this ratio increased above unity. For a ratio of 2.75, they observed that Γ changed significantly after 50% dissolution. This is exemplified in Figs. 12.11 and 12.12.

SYMBOLS

A = surface area of a plane

b = (a) breadth or (b) size of a dissolving particle

b_0 = original (a) breadth or (b) size of a dissolving particle

D = diffusion coefficient

d = general term for the size of a particle

$$y = -1.0795e-2 + 4.4607e-2x \quad R^2 = 0.999$$

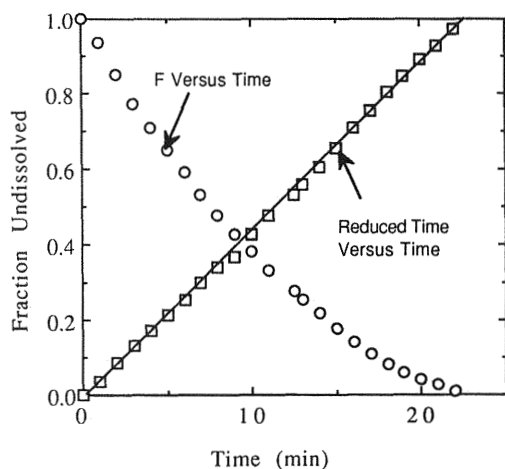


Fig. 12.11 Fraction retained [see Eq. 12.86] and reduced time [see Eq. 12.74] as a function of time of dissolution of a potassium dichromate crystal of dimensions $l_0 = 1.120$ cm, $b_0 = 0.518$ cm, and h_0 cm. (Data from Dali, 1997.)

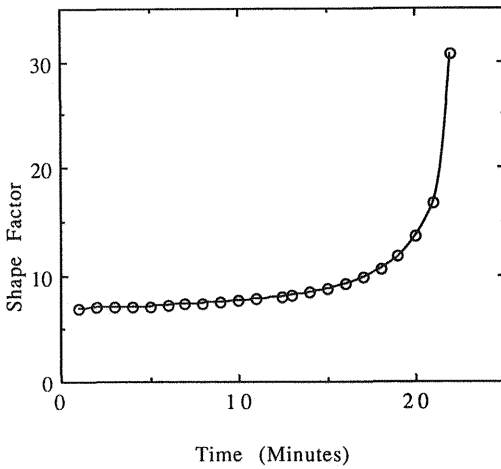


Fig. 12.12 Shape factor as a function of dissolution time of a potassium dichromate crystal of dimensions $l_0 = 1.120$ cm, $b_0 = 0.518$ cm, and h_0 cm as a function of dissolution time. (Data from Dali, 1997.)

h = (a) thickness of film layer (b) height of a crystal

J = flux

$K = 2kS/\rho$ = cube-root dissolution rate constant for a cube

$K_v = k\Gamma S/3\rho$ = cube-root dissolution rate constant for a particle with a shape factor of Γ

$K_{mn} = N^{1/3}k\Gamma S\rho^{-2/3}/3$ = cube-root dissolution rate constant for a population of N particles

$K'_{mn} = (k\Gamma S)N^{1/3}\rho^{-2/3}M_0^{-1/3}/3$ = relative cube-root dissolution rate constant for a population of N particles

k = intrinsic dissolution rate constant

k_b = intrinsic dissolution rate constant in b -direction

k_h = intrinsic dissolution rate constant in h -direction

k_L = intrinsic dissolution rate constant in L -direction

L = length of a crystal

M = mass of a population of monodisperse particles

M_0 = original mass of a population of monodisperse particles

m = mass not dissolved at time t for a single particle

m_0 = original mass of a single particle

$p = L_0/h_0$

Q = mass flow rate (cm^3/s)

$q = b_0/h_0$

s = surface area of a single particle

S = solubility

t = time

u = reduced time

V = volume of liquid

$V_x(y)$ = linear velocity Q (cm^3/s)

y = direction perpendicular to a dissolving surface

α_s = surface shape factor of a particle

α_v = volume shape factor of a particle

β = constant in the flow conversion equation

Γ = shape factor

ρ = density

REFERENCES

- Carstensen JT (1974). In: Leeson L, Carstensen JT, eds. *Dissolution Technology*. The Academy of Pharmaceutical Sciences. American Pharmaceutical Association, Washington, DC, p 5.
- Chen LR, Grant DJW (1998). *Pharm Dev Technol* 4:487.
- Dali M (1997). PhD dissertation, University of Wisconsin, Madison, WI.
- Dali MV, Carstensen JT (1996). *Pharm Res* 13:155.
- Dallavalle JM (1948). In: *Micromeritics*, 2nd ed. Pitman Publishing, New York, p 142.
- Grant DJW, Medhizadeh M, Chow AHL, Fairbrother JE (1984). *Int J Pharm* 18:25.
- Guillory K (1992). Personal Communication.
- Iba K, Arakawa E, Morris T, Carstensen JT (1991). *Drug Dev Ind Pharm* 17:77.
- Lai TY-F, Carstensen JT (1978). *Int J Pharm* 1:33.
- Levich VG (1962). *Physicochemical Hydrodynamics*. Printice Hall, Englewood Cliffs, NJ, pp 87–116.
- Lu ATK, Frisella ME, Johnson KC (1993). *Pharm Res* 10:308.
- Noyes A, Whitney W (1897). *J Am Chem Soc* 23:689.
- Okonogi S, Oguchi T, Yonemochi E, Puttipatkhachorn S, Yamamoto K (1997). *Int J Pharm* 156:175.
- Pedersen PV, Brown KF, (1976). *J Pharm Sci* 64:1981.
- Rao MR, Lin M, Larive CK, Southard MZ (1997). *J Pharm Sci* 86:1132.
- Riegelman S (1979). *Dissolution testing in drug development and quality control*. The Academy of Pharmaceutical Sciences, Task Force Committee, American Pharmaceutical Association, p 31.
- Shah AC, Nelson KG, (1975). *J Pharm Sci* 64:151824.

13

Dissolution from Polydisperse Populations

13.1. Dissolution of Polydisperse Powders	209
13.2. Particle Size Distributions and Dissolution	210
13.3. Dissolution After the Critical Time, t^*	217
13.4. Effect of Medium	219
Symbols	220
Appendix	221
References	221

13.1. DISSOLUTION OF POLYDISPERSE POWDERS

If powders are polydisperse, then if the population is “infinite,” that is starting at size zero (with an infinitely small probability or fraction) and on the high side ending at an infinite large size (again with an infinitely small probability or fraction), then it is possible to solve dissolution patterns in closed form.

As we will see in the following, a more realistic powder population is one in which there is a finite, smallest particle and a finite largest particle (Fig. 13.1), and for such systems the type of dissolution pattern of the *type* in Eq. (12.48) (i.e., a cube-root law adherence) will prevail.

Carstensen and Musa (1972) applied simulation to a truncated lognormal distribution of spherical particles to the principles of dissolution, and this was followed up by a solution in closed form by Brooke (1973, 1974). In the latter case, three additional assumptions were made: namely, that (a) the smallest particle was zero size; (b) the expression for the distribution remained correct during the dissolution process; and (c) a number-based lognormal distribution would also be lognormal after transformation by the Hatch–Choate equation.

Brooke (1973, 1974) arrived at the conclusion that for a polydisperse, lognormal powder, the plot of amount retained versus time would follow a cube-root equation, but the slope would be inversely proportional to $\ln[\sigma]$. This was confirmed experimentally by Carstensen and Patel (1975) who found that, approximately

Size

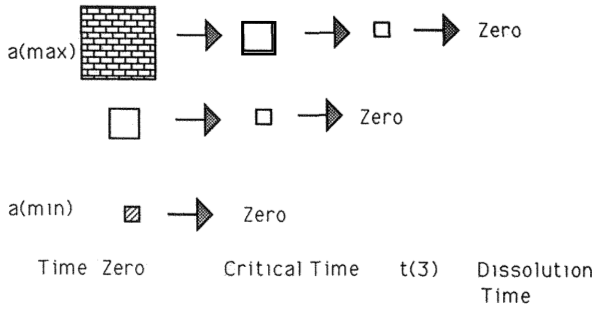


Fig. 13.1 The situation in the dissolution of a polydisperse powder.

$$1 - [M/M_0]^{1/3} = K/[b_{gm} \exp(-3\{\ln^2 \sigma\})] \quad (13.1)$$

where b_{gm} is the geometric mean of the particle population and $\ln[\sigma]$ is its standard deviation.

13.2. PARTICLE SIZE DISTRIBUTIONS AND DISSOLUTION

Particulate solids resulting from unit processes such as crystallization, precipitation, and milling, exhibit skewed particle size distributions (Carstensen and Rodriguez-Hornedo, 1985; Steiner et. al., 1974; Carstensen and Patel, 1975).

The importance of particle size distribution of powder substances for dissolution rates has been well documented in the pharmaceutical literature (Carstensen and Musa, 1972; Brooke, 1973, 1974; Higuchi and Hiestand, 1963; Higuchi et al., 1963; Hintz and Johnson, 1989 Pedersen and Brown, 1975). Simply said, smaller particles dissolve at a faster rate than larger particles.

Although very treatable from a theoretical point of view, there are practical problems that are associated with particle size distribution and dissolution. In today's climate, virtually all solid-dosage form products are routinely subjected to dissolution testing, and the most common cause for product recalls is failure of a product to meet dissolution specifications (Cabana and O'Neil, 1980). Most often, particle size limits are included in drug substance specifications, because particle size affects both dissolution characteristics and machinability (flow or compression) of the substance. However, most particle size distributions are derived from volume-based measurements (e.g., Coulter counter) of the particles from a random sample and suffer from the fact that (a) the volume is converted to an equivalent spherical radius, and (b) that the sample size is always very small. Barnett and Nyström (1982) have cautioned researchers about the misuse of the spherical approximation by stating that, "...direct comparisons between microscope-derived mean particle size parameters and Coulter-counter-derived data can lead to erroneous conclusions if no consideration is given to the shapes of particles...." (Houghton and Amidon, 1991). Size determination of needle-shaped particles by techniques such as a Coulter counter can lead to experimental difficulties such as "coincidence" of two or more particles at the orifice leading to faulty results. It further has the disadvan-

tage that it does not directly address the main reason for its execution: namely, dissolution in a *USP* dissolution apparatus.

Microscopy will yield information about the *actual* dimensions of nonspherical particles. In this, a particular dimension (length, breadth, Ferret diameter) is selected, and a certain number of particles examined, and classified in size ranges. The numbers in the ranges may be converted to fraction of particles, and the curve may be normalized, as shown in Fig. 13.2, so that the area under the curve (AUC) is unity.

The major advantage of this method is that it can furnish size as well as shape information about nonisometric solids. On the other hand, the inherent tediousness and time-consuming nature of this procedure limits its use. Also, the user is restricted to a relatively small sample size, based on which the representativeness of the powder population has to be relied. Houghton and Amidon (1991) have suggested a microscopic-based image analysis routine procedure to have a check on the lot-to-lot variability in the particle size and shape characteristics of three lots of an investigational drug (Houghton and Amidon, 1991). Invariably, such methods rely on the particular software-defined size and shape parameters. Powder dissolution of polydisperse samples can be used, with distinct advantage, to obtain meaningful information on particle size distribution of crystalline substances of nonspherical nature (Dali, 1997).

If a particle has an initial breadth b_0 , and volumetric shape factor α_{v0} then the original mass, m , of that particle is given by

$$m = \rho v = \rho(\alpha_{v0})b_0^3 \quad (13.2)$$

where v is volume, and ρ is particle density. It is possible, by microscopy, to determine two of the three dimensions and to plot these by a normalized frequency function $f(b_0)$, so the number fraction N_b of particles between the infinitesimally small interval $(b_0, b_0 + db_0)$ would be given by

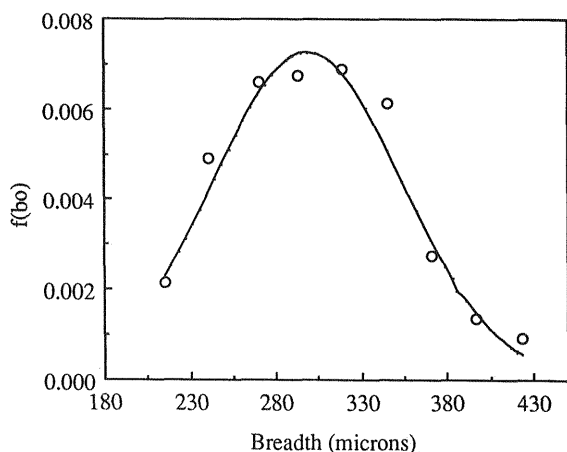


Fig. 13.2 Frequency distribution function of a $-40/+50$ sieve fraction of oxalic acid dihydrate.

$$N_b = f(b_0)db_0 \quad (13.3)$$

Denoting the initial mass of the whole powder population by M_0 , it would given by

$$M_0 = \int_{b_{\min}}^{b_{\max}} \{N\rho f(b_0) (\alpha_{v0})b_0^3\}db_0 \quad (13.4)$$

$b_{\max}$ and $b_{\min}$ here denote the largest and smallest dimension of the particles in the powder population and b_0 has reference to the fact that the particles will be placed in a dissolution medium at a given time of zero. Equation (13.4) applies to a polydisperse system of particles (for instance, a sieve fraction), and an average value for the initial volume shape factor has been ascribed to that particular sieve fraction.

If the powder is dissolved under sink conditions, then the dimensions of the particle will decrease linearly with time (Carstensen and Musa, 1972; Dali and Carstensen, 1996; Edmundson and Lees, 1965; Schoonen et al. 1979).

$$b = b_0 - Kt \quad (13.5)$$

Note that the initial distribution function can be used to calculate the mass undissolved until the critical time t^* . It is at the critical time that the smallest particle disappears from the dissolution medium, and up to this point in time (t^*), the total number of particles in the system remains the same (Carstensen and Musa, 1972; Carstensen and Patel, 1975; Dali, 1997). If the powder is allowed to dissolve then, at times $t < t^*$, the mass undissolved will be

$$M = \int_{b_{\min}}^{b_{\max}} \{N\rho f(b_0) (\alpha_{v0})(b_0 - Kt)^3\}db_0 \quad (13.6)$$

If the cubed term is expanded, then

$$M = A_1 - B_1t + C_1t^2 - D_1t^3 \quad (13.7)$$

where the coefficients A_1 , B_1 , C_1 , and D_1 are elaborated on in the following. An example is shown in Fig. 13.3.

$$A_1 = N\rho\alpha_{v0} \int_{b_{\min}}^{b_{\max}} f(b_0)b_0^3 db_0 = N\rho\alpha_{v0} \mu_3 \quad (13.8)$$

This term is obviously the original mass of the powder sample and μ_3 is the third moment of the probability distribution function (Bennett and Franklin, 1961). The third coefficient in Eq. (13.8) is

$$C_1 = 3N\rho K^2 \alpha_{v0} \int_{b_{\min}}^{b_{\max}} f(b_0)b_0 db_0 = 3K^2 N\rho\alpha_{v0} \mu_1 \quad (13.9)$$

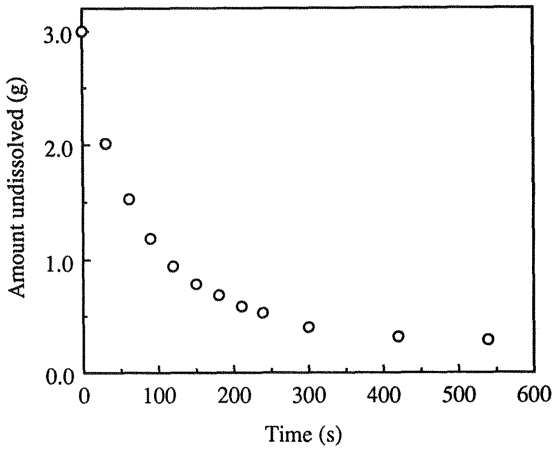


Fig. 13.3 Amount undissolved for the dissolution of a -40/ + 50 sieve fraction of oxalic acid dihydrate in 0.1 N HCl at 25°C and 50 rpm.

Where μ_1 is the first moment of the probability density function and also the mean of the distribution (Bennett and Franklin, 1961). The second coefficient in the expansion is

$$B_1 = 3N\rho K\alpha_{v0} \int_{b_{\min}}^{b_{\max}} f(b_0) b_0^2 db_0 = 3K N\rho\alpha_{v0} \mu_2 \quad (13.10)$$

where μ_2 is the second moment of the probability density function (Bennett and Franklin, 1961). The variance of the powder population is given by

$$s^2 = \mu_2 - \mu_1^2 \quad (13.11)$$

The coefficient to the last term is given by

$$D_1 = N\rho K^3\alpha_{v0} \int_{b_{\min}}^{b_{\max}} f(b_0) db_0 = K3N\rho\alpha_{v0} \quad (13.12)$$

where use has been made of the fact that the probability density function as used is normalized, *i.e.*,

$$\int_{b_{\min}}^{b_{\max}} f(b_0) db_0 = 1 \quad (13.13)$$

Equation (13.7) may be divided through by $A_1 = M_0$, after which it takes the form:

$$M/M_0 = 1 - B_2t + C_2t^2 - D_2t^3 \quad (13.14)$$

and the coefficients with subscript “2” are then the coefficients with subscript “1” divided by M_0 .

The coefficients of the terms in t , t^2 , and t^3 in Eq. (13.14) are given by the following equations:

$$B_2 = 3K\mu_2/\mu_3 \quad (13.15)$$

$$C_2 = 3K^2\mu_1/\mu_3 \quad (13.16)$$

$$D_2 = K^3/\mu_3 \quad (13.17)$$

In a typical research and development setting, in the event that a new drug candidate is recognized by the drug discovery group, then the dissolution rate constant K , for that compound under specified hydrodynamic conditions can be determined from powder dissolution data and particle size analysis by microscopy (Dali, 1996). This can be done with Eqs. (13.14) through (13.17). From the dissolution data, the coefficient B_2 is obtained and through the results from microscopy the moments μ_2 and μ_3 can be evaluated. Similarly, from Eqs. (13.2) through (13.4), by knowing N , the initial number of particles, and the density of the solid, the average initial volume shape factor for a polydisperse powder can be estimated (Dallavalle, 1948). Dissolution studies and particle size analysis on three sieve fractions of oxalic acid dihydrate: $-30/+40$; $-40/+50$; and $-50/+60$, yielded a K value of $(1.42 \times 0.19) \times 10^{-4}$ cm/s when dissolution was carried out in 0.1 N HCl in a *US P* paddle apparatus at 25°C and 50 rpm. The K value should be independent of particle size. The results for volume shape factor obtained by two methods are quite comparable.

The same problem can be considered in the opposite direction (Carstensen and Dali, 1998). With the knowledge of K value for a compound (for instance oxalic acid dihydrate) under specified hydrodynamic conditions, the fraction undissolved as a function of time, the moments of the distribution function of a “dimension of significance” can be obtained. Only the dissolution data up to the critical time are utilized in this manner (Fig. 13.4). At the critical time, there is a change in slope

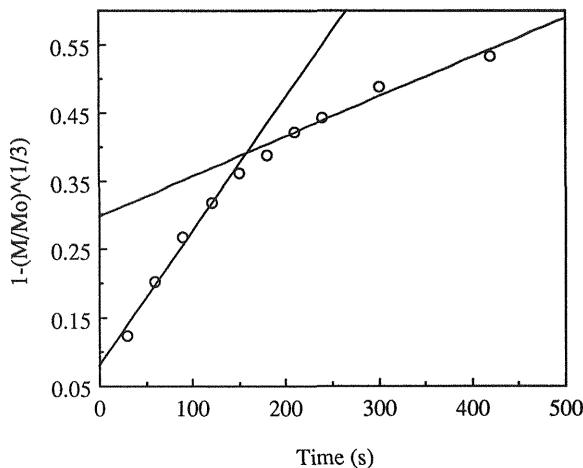


Fig. 13.4 Cube-root law plot for the dissolution of a $-40/+50$ mesh fraction of oxalic acid dihydrate showing the critical time.

in the cube-root law plot (Hixson and Crowell, 1931; Carstensen and Patel, 1975). The fraction undissolved data until the critical time can be least-square-fitted to a third-degree polynomial in time as dictated by Eq. (13.14). The moments of distribution, μ_1 , μ_2 , and μ_3 can be evaluated from Eqs. (13.15) through (13.17), with three equations used to solve for three unknowns.

To obtain an estimate of a K value for for a compound (e.g., oxalic acid dihydrate), the moments of the distribution function had to be known. Thus the restriction of breadth being the defining dimension was imposed on the integrals before they could be evaluated numerically. In the process of working backward, to obtain the distribution parameters from powder dissolution data, the integrals that define the moments of distribution function are allowed to “float.” In other words no restriction on the kind of dimension is imposed at this point. So it is of interest to determine which of the three dimensions of the particle is perceived by this approach. The discussion pertaining to this aspect will be resumed subsequently.

Carstensen and Dali (1998), to exemplify these ideas, carried out dissolution of three sieve fractions of oxalic acid dihydrate. For these sieve fractions the distribution parameters for the lengths and breadths of the particles were known. This was necessary to have assurance about the validity of the approach.

Figure 13.3 shows the dissolution curve for a $-40/+50$ mesh fraction of oxalic acid dihydrate. The cube-root law plot for the same event is shown in Fig. 13.4 from which an estimate of the critical time was obtained. From the least-square-fit to the data the coefficients of terms in t as per Eqs. (13.4) through (13.7) can be obtained.

The mean and standard deviation for a particular sieve fraction can be calculated using the following equations:

Mean = μ_1

(13.18)

The results for the three sieve fractions are shown in Table 13.1 and Fig. 13.5. The mean and standard deviation obtained are compared with those for the breadth of the particles from respective sieve fractions obtained from microscopy. In all the three sieve fractions, the mean obtained directly from dissolution data is less than the mean from microscopy. In the wake of this observation, the following question arises: Is it possible, by not imposing any restrictions about the dimension of the

Table 13.1 Distribution Parameters for Sieve Fractions of Oxalic Acid Dihydrate Determined from Dissolution Data and Comparison with Those Obtained from Microscopy

Sieve fraction	$\mu(b_0)$ from microscopy (μm)	σ_b from microscopy (μm)	Mean from dissolution (μm)	Standard deviation from dissolution (μm)	$n =$ mean (h_0/b_0)	Predicted $\mu(h_0)$ (μm)
$-30/+40$	410	85	222	84	0.56	230
$-40/+50$	299	55	167	70	0.47	140
$-50/+60$	240	32	120	33	0.47	113

Source: Carstensen and Dale, 1998.

Table 13.2 Third Derivatives of Dissolution Curve in Fig. 13.6

Time	d^3M/dr^3
0	
30	-0.30
60	0.00
90	0.10
120	-0.30
150	-0.10
180	0.00
210	
240	

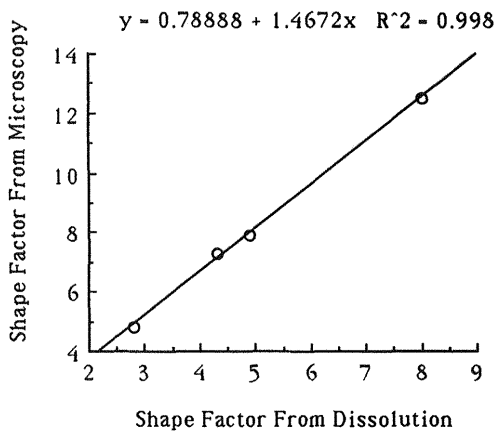


Fig. 13.5 Correlation between microscopically and dissolution-determined shape factors.

$y = 5.0046 - 3.5459e-2x + 1.2648e-4x^2 - 1.8768e-7x^3 \quad R^2 = 1.000$

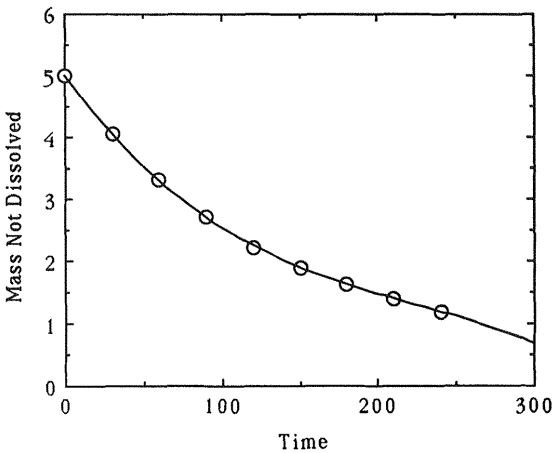


Fig. 13.6 Mass undissolved for the dissolution of a 5-g 30/40-mesh fraction of oxalic acid dihydrate.

particles on the integrals comprising the moments of distribution, that the smallest dimension (height) of the particles is recognized? To answer this query, the authors resorted to the volume shape factor data for these sieve fractions that were obtained microscopically (see Table 13.1 and Fig. 13.5). The ratio of mean height to the mean breadth can be calculated from the volume shape factors obtained from microscopy and dissolution. Thus the mean of height ($Mh_0 = Mb_0$) for particles belonging to a particular sieve fraction can be predicted. These values can be compared with the means obtained directly from dissolution data (Fig. 13.6). As shown in Table 13.1, these two set of values are in excellent agreement. Also the standard deviations of the breadth of particles are comparable with those obtained from dissolution.

It is seen from Eq. (13.14) that the third derivative should be independent of time. That this is (approximately) so is shown in Fig. 13.7.

It is obvious that the longer the precritical time is, the better the assessment of the coefficients. It is natural to carry out the dissolution in water, but just for the purpose of determination of distribution parameters, other solvents and apparatuses may be used. If a solvent exerting less solubilizing power on the substance is used, or an apparatus allowing slower dissolution is employed, then longer time intervals prior to t^* may be used, thereby improving precision. If however, the value of (aqueous) K is sought under *USP* type dissolution apparatus conditions, then this apparatus should be used, and water, N/10 hydrochloric acid or simulated gastric fluids could be used as the dissolution media.

13.3. DISSOLUTION AFTER THE CRITICAL TIME, t^*

After the smallest particle has dissolved, the model for dissolution must, by necessity, change.

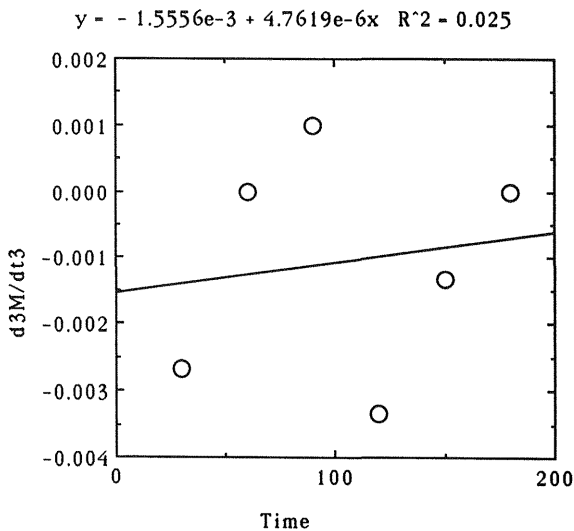


Fig. 13.7 Third derivative from data from a dissolution run of a 30/40 mesh cut of oxalic acid dihydrate.

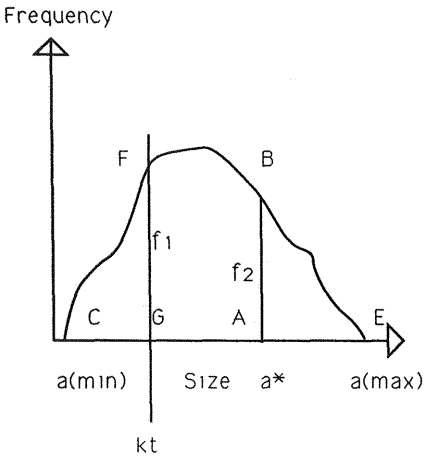


Fig. 13.8 Schematic of dissolution of a multiparticulate.

Consider a (normalized) distribution shown as an example in Fig. 13.8. The distribution shown is that of the powder before dissolution, and, for instance a particle of size a^* has a frequency denoted f_2 (the length of the chord AB). The number of particles of this size is N times f_2 where N is the total number of particles in the population. After a given time t , all the particles will have become smaller by an amount of $[kt]$ (i.e., the particles originally of size a^* would have a size of $a^*-[kt]$, but the number of the particles would still be f_2N). The smallest particle after a time of t would be kt (point G) a particle just about to disappear (or just disappeared). The number of particles at this point would be $[kt]f_1$, where f_1 is the number denoted by the chord FG . Assuming a cubical particle, the mass remaining M , after dissolution has taken place for a time of t , is, therefore,

$y = -0.29233 + 2.3933e-3x - 4.0376e-6x^2 \quad R^2 = 0.866$

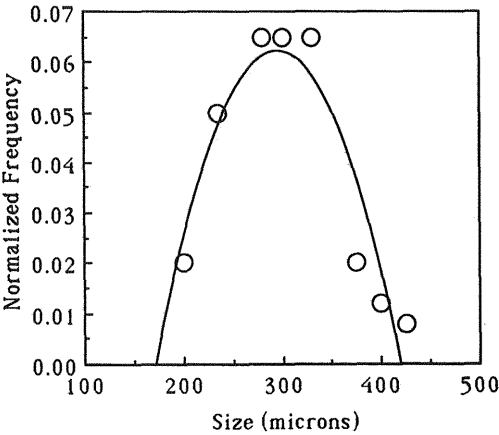


Fig. 13.9 Parabolic approximation of particle population.

$$M = N\rho\alpha_v \int_{kt}^{a_{\max}} f(a)[a - kt]^3 da \quad (13.19)$$

where $t > t^*$ (i.e., larger than the critical time). A procedure similar to the one in the previous sections is not possible in this instance because the lower limit is not a given size.

$f(a)$ is usually, for populations, taken as either normal or lognormal, but it has been seen in Fig. 13.2 that, for a sieve cut, it is at best normal. In fact the data shown in Fig. 13.2 are more likely to fit a second-degree polynomial (Fig. 13.9). If

$$f(a) = j_1 + j_2a + j_3b \quad (13.20)$$

is inserted in Eq. (13.19) then a *sixth-degree polynomial in t* results. (This is shown in the Appendix). Dissolution curves beyond t^* should, therefore, be plottable in this fashion.

Because there is always a nick in the curve at short times, it is possible to assign values to both $a_{\min}$ and $a_{\max}$. In particular the latter can be obtained easily by the point where the curve intersects with the x -axis.

13.4. EFFECT OF MEDIUM

Water or aqueous solvents as a dissolution medium have tacitly been assumed to be the case in the preceding writing.

There are examples for which the solubility of a compound is sufficiently low that normal USP volumes (900 mL) are insufficient to dissolve all the solid, and there are three principles that are used to compensate for this: (a) the use of surfactants may sufficiently increase the solubility so that meaningful dissolution can be carried out, or (b) a mixed solvent may be used, or (c) the use of complexation may be employed. In work by Diaz et al. (Fig. 13.10), dealing with the

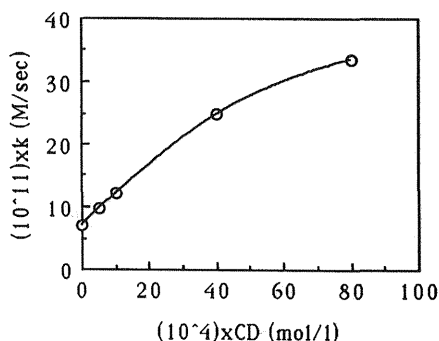


Fig. 13.10 Dissolution rate constants (in M/s) of albendazole as a function of cyclodextrin concentration (CD). (Data from Diaz et al., 1998.)

* The authors employ 1 mg/2.5 mL of water, which is far above the solubility of the compound, so that the amount of mass dissolved in this experiment is also insufficient to change the surface area.

complexation of albendazole with cyclodextrins, it was found that the purely aqueous solubility S_0 , increased to a total solubility of S_t at a given ligand concentration of L_t . The authors tested the dissolution under sink conditions (the initial parts of their curves) and constant surface area* and found dissolution to be fairly linear in time.

$$C = (kASL_t/V)t \quad (13.21)$$

where A is area, S_t is the solubility at the ligand concentration in question L_t , and V is the dissolution volume. If k were independent of the ligand (i.e., of the medium), then the slopes of these lines should be proportional to S_t , since A and V are constant. Since S is linear in L_t , the slopes should be linear in $[L_t]$, but as seen in the figure they are not.

SYMBOLS

A = surface area

$a_m = a_{\max}$ = size(length, breadth, or width) of largest particle

$a_0 = a_{\min}$ = size(length, breadth, or width) of smallest particle

A = surface area of the dissolving solid at time t

b = width of a particle

b_{gm} = geometric mean of a lognormal particle population

B = width of channel for dissolution study

C = concentration

$f(b)$ = normalized frequency function for the width of a particle

h = height of a particle

m = mass of an undissolved particle

M = multiparticulate undissolved mass

M_0 = initial multiparticulate mass before dissolution

k = intrinsic dissolution rate constant (cm/s)

K = linear (cube-root) dissolution rate constant

N = number of particles in a multiparticulate sample

Q = a constant

r = radius of particle

R = the gas constant

s = standard deviation of sizes in a particle population

$\ln[s]$ = standard deviation of a lognormal particle population

S = solubility

S_L = ligand solubility in the presence of substrate

t = time (of dissolution)

t^* = critical time

T = absolute temperature,

V = volume of dissolution medium

α_{v0} = volume shape factor

κ = Boltzmann constant

μ_1 = mean (first-moment) of a particle population

μ_2 = second-moment of a particle population

μ_3 = third-moment of a particle population

ρ = particle density

APPENDIX

In this section, it is assumed that particle size distribution data exist and may be approximated by a parabola, as shown in Fig. 13.9. The parabola is expressed in equation form as:

$$f = j_0 + j_1 a + j_2 a^2 \quad (13A.1)$$

If the distribution is known, then the values of j_0, j_1 and j_2 are known from the following facts. For convenience, the maximum and minimum diameters are denoted a_m and a_0 . The maximum frequency occurs at f_3 and is zero at the extremes

$$f_3 = \{j_1(a_0 + a_m)/2\} + j_2\{(a_0 + a_m)^2/4\} + j_0 \quad (13A.2)$$

$$0 = j_0 + j_1 a_0 + j_2 a_0^2 \quad (13A.3)$$

$$0 = j_0 + j_1 a_m + j_2 a_m^2 \quad (13A.4)$$

With knowledge of f_3 , $a_0(a_{\min})$ and $a_1(a_{\max})$ the values of j_0, j_1 , and j_2 may be calculated. The amount remaining at time $t > t^*$ is the value of the integral:

$$\begin{aligned} M/\{\rho\alpha_v\} &= \int_{kt}^{a_m} f(a)(a - kt)^3 da \\ &= \int_{kt}^{a_m} \{j_0 + j_1 a + j_2 a^2\}(a^3 - 3a^2(kt) + 3a(kt)^2 - (kt)^3) da \end{aligned} \quad (13A.5)$$

The lower integration limit is (kt) , rather than zero or $a_{\min}$ for reasons stated in the text. The integral has a solution of the following type:

$$M = M_0 + \phi_1(kt) + \phi_2(kt)^2 + \phi_3(kt)^3 + \phi_4(kt)^4 + \phi_5(kt)^5 + \phi_6(kt)^6 \quad (13A.6)$$

where the coefficients are given by the following:

$$\phi_6 = j_2\{-(1/6) + (3/5) - (3/4) + (1/3)\}j_2 = 17j_2/60 \quad (13A.7)$$

$$\phi_5 = j_1\{-1/5 + 3/4 - 1 + 1/2\} = j_2/20 \quad (13A.8)$$

$$\phi_4 = j_0\{(1/4) + 1 - (3/2) + 1\} = j_0 \quad (13A.9)$$

$$\phi_3 = -\{(j_2/3)a_m^3 + (j_1a_m^2) + j_0a_m\} \quad (13A.10)$$

$$\phi_2 = (3j_2a_m^4/4) + j_1a_m^3 + (3j_0a_m^2/2) \quad (13A.11)$$

$$\phi_1 = -\{(3j_2a_m^5/5) + (3j_1a_m^4/4) + j_0a_m^3\} \quad (13A.12)$$

$$\phi_0 = M_0 = (j_2a_m^6/6) + (j_1a_m^5/5) + j_0a_m^4 \quad (13A.13)$$

REFERENCES

Barnett MI, Nystrom C (1982). Pharm Technol 6:49.

- Bennett CA, Franklin NL (1961). *Statistical Analysis in Chemistry and the Chemical Industry*. John Wiley & Sons, New York.
- Brooke D (1973). *J Pharm Sci* 62:795.
- Brooke D (1974). *J Pharm Sci* 63:344.
- Cabana BE, O'Neil R (1980). *Pharm Forum* 6:71.
- Carstensen JT (1966). *Modeling and Data Treatment in the Pharmaceutical Sciences*. Technomic, Lancaster, PA.
- Carstensen JT, Dali MV (1998). *Drug Dev Ind Pharm* 24:637.
- Carstensen JT, Musa MN (1972). *J Pharm Sci* 61:223.
- Carstensen JT, Patel M (1975). *J Pharm Sci* 64:1770.
- Carstensen JT, Rodriguez-Hornedo N (1986). *J Pharm Sci* 74:1322.
- Dali MV, (1997). PhD dissertation, University of Wisconsin-Madison.
- Dali MV Carstensen JT (1996). *Pharm Res.* 13:155.
- Dallavalle JM (1948). In: *Micromeritics*, 2nd ed. Pitman Publishing, New York, p 142.
- Diaz D, Bernard MJB, Mora JG, Lianos CME (1998). *Pharm Dev Technol* 3(3):395.
- Edmundson IC, Lees KA (1965). *J Pharm Pharmacol* 17:193.
- Higuchi WI, Hiestand EN (1963). *J Pharm Sci* 52:67.
- Higuchi WI, Rowe EL, Hiestand EN (1963). *J Pharm Sci* 52:163.
- Hintz RJ, Johnson KS (1989). *Int J Pharm* 51:9.
- Hixson A, Crowell J (1931). *Ind Eng Chem* 23:923.
- Houghton ME, Amidon GE (1991). *Pharm Res* 9:856.
- Pedersen PV, Brown KF (1976). *J Pharm Sci* 64:1981.
- Schoonen GW, de Vries-Nijboer T, Huizinga (1979). *J Pharm Sci* 68:163.
- Steiner G, Patel M, Carstensen JT (1974). *J Pharm Sci* 63:1395.

14

Solid-State Stability

14.1. Random Decomposition: Amorphates—Spontaneous Reactions in the Crystalline Phase	224
14.2. Topochemical Reactions	228
14.3. The Avrami–Erofeyev Equations	230
14.4. Nucleation Followed by Fast Kinetics (Polymorphic Transformations)	234
14.5. Surface Nucleation (Prout–Tompkins Model)	234
14.5.1. The solid to solid-plus-gas reaction	235
14.5.2. Temperature dependence of the solid to solid-plus-gas reaction	238
14.6. The Ng Equation	239
14.7. The Solid to Liquid-plus-Gas Reaction	240
14.8. Diffusion Controlled Interactions	245
14.9. General Interactions in Dosage Forms	249
14.9.1 Tartaric acid and sodium bicarbonate	250
14.10. pH of the Microenvironment	254
14.11. Pseudopolymorphic Transformations	255
14.12. Equilibria and Effects of Applied Pressure	256
14.13. Photolysis in the Solid State	256
14.14. Choice of Model	256
14.15. Interactions Involving a Liquid Phase	257
14.16. Cases of Interaction of a Liquid with a Poorly Soluble Drug	261
14.17. Reactions via the Gas Phase	261
Symbols	262
References	263

The subject of solid-state stability is of great importance in pharmaceuticals. Stability patterns of solid dosage forms are partly a function of the stability of the drug substance in the dosage form, but also, as shall be seen in the Chap. 15, a function of moisture.

14.1. RANDOM DECOMPOSITION: AMORPHATES—SPONTANEOUS REACTIONS IN THE CRYSTALLINE PHASE

It can be shown, as is to be described (Carstensen and Morris, 1993), that reactions in the rubbery amorphous state are akin to solution kinetics. Amorphous materials, as shown by Carstensen and Morris (1989), are less chemically stable than their crystalline counterparts. This has also been demonstrated by Imaizini et al. (1980) and by Gubskaya et al. (1995). Reactions in the crystalline state can be attributed to the presence of moisture or light, but solids may also undergo decomposition or solid-state reactions in the “dry” state (i.e., without the interference of water or light) (Carstensen, 1980; Byrn et al., 1996). For instance Shalaev et al. (1997) have shown parallel reactions occurring in the solid-state methyl transfer of tetracycline methyl ester because fitting of the data gives good biexponential fits. They attribute this to (a) presence of an amorphous phase (if material has been milled or freeze-dried), or (b) that processing “increases the extent of disorder in the remaining crystal lattice,” and associate this with different types of lattice defects. The parallel reactions (i.e., the amorphous versus the defect pathway) give rise to the same reaction products.

The most interest and the largest body of work of amorphates is in the field of macromolecules. These usually possess a glass transition temperature T_g , and the states are referred to as “glassy” below (the highest T_g in multiple glass transition temperatures) and “rubbery” above T_g .

Only a few articles have appeared in the literature on the subject of chemical stability of amorphates. In general, a compound is more stable in the crystalline state than in an amorphous state, but exceptions exist (Suknik et al., 1975, O'Donnell and Whittaker, 1992; Stacey et al., 1959). There *are* examples that have been reported (Lemmon et al., 1958) for which the crystalline state is less soluble than the molecule in solution, but they are rare.

In general, in a crystalline state, molecules are, to a great extent, fixed in position. If the situation exists where a group from one molecule reacts with another group in a neighbor, the situation, as shown in Fig. 14.1, arises.

Pothisiri and Carstensen (1975) have shown that, in a situation such as with substituted benzoic acids, the decomposition is between two groups in the same molecule.

Suppose parts A and B of the molecule depicted in Fig. 14.1 react. If this occurs, arrangement C would give better stability than arrangement D, because A would be farther away from B in the former arrangement. Arrangement D can also be more adverse than a random orientation, and if that is true, then the amorphous form would be more stable than the crystalline (arrangement D). This is the exception, rather than the rule.

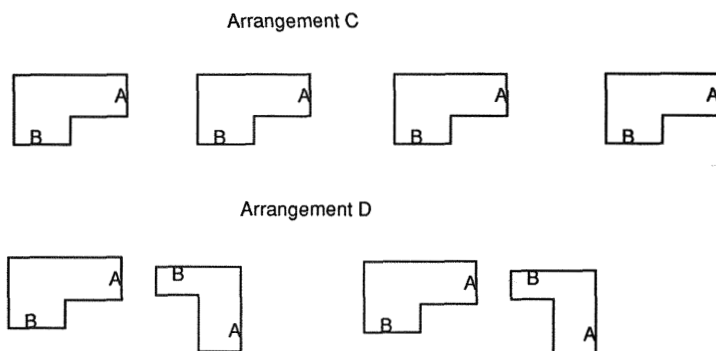


Fig. 14.1 Different possible arrangements of a molecule in the solid state, implying different distance between possibly interacting groups (A and B).

In the presence of moisture, conversions from amorphous to crystalline modifications are promoted (Carstensen and Van Scoik, 1990; Van Scoik and Carstensen, 1990) and the material developed in the following all refers to anhydrous conditions.

In the work by Carstensen and Morris (1993), amorphous indomethacin was produced by melting a crystalline form of it to above melting (162°C) and recooling it to below 162°C . Amorphates made in this manner are morphologically stable down to 120°C so that their chemical stability can be monitored (If the temperatures are lowered rapidly, then stable amorphates can be formed at room temperature, but kinetics cannot be followed easily because of the slow reaction rate at room temperature.) At a range of temperatures below this temperature crystallization occurs too rapidly to permit assessment of amorphous stability. Amorphous samples were placed at several constant temperature stations (145, 150, 155, 165, 175, and 185°C) and assayed from time to time. The content of intact indomethacin was assessed by using the U.S. Pharmacopeia (*USP*) method of analysis.

The decomposition curves of amorphous indomethacin and a melt of indomethacin at different temperatures is shown in Figs. 14.2 and 14.3. The pattern is strictly a first-order one. Of the few reports in literature dealing with the chemical stability of compounds in the amorphous state, amorphous cephalosporins (Pfeiffer et al., 1976; Oberholtzer and Brenner, 1979; Pikal et al., 1977) also adhere to a first-order pattern. One purpose of the following writing is to seek an explanation for this pseudo-first-order (or indeed, truly first-order) pattern. The explanation must lie, in some manner, with the fact that in the rubbery state, the molecules can arrange themselves in a random fashion, in a somewhat frozen (or much slowed) manner of that of the melt above the traditional melting point.

The results obtained from the melt are shown in Fig. 7.1, and as seen a first-order plot results. If an Arrhenius plot is drawn of the data from 14.2, then Fig. 14.3 results.

It is seen that the Arrhenius plot of the amorphate continues into the Arrhenius plot of the melt. An attempt to explain this is made in the following.

If the substance in Fig. 14.1 was a crystalline solid, then the potential energy between molecules would be inversely proportional to a power function of their

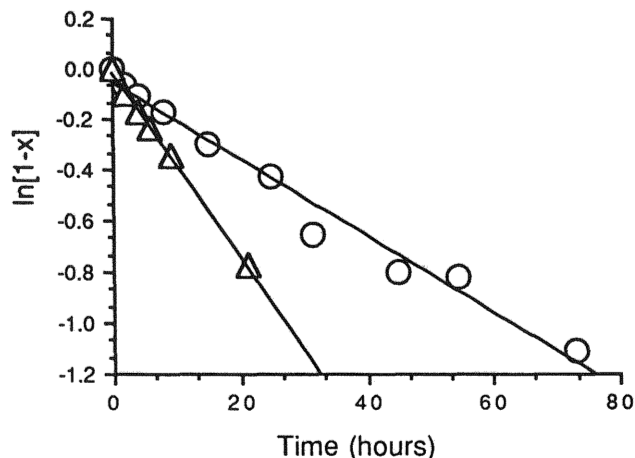


Fig. 14.2 Decomposition of amorphous indomethacin: Symbols; o, 145°C ($k = 0.015 \text{ h}^{-1}$); Δ , 155°C ($k = 0.036 \text{ h}^{-1}$). (Data from Carstensen and Morris, 1993.)

distance (the lattice constant) (Carstensen and Morris, 1993); that is, it would be akin to a Lennard–Jones potential (Lennard–Jones, 1931). However, in the amorphous state, if the decomposition is an intermolecular (rather than an intramolecular) reaction, then a group A in molecule a interacts with group B in the neighboring molecule b. The energy of the molecular pair will be dependent on the distance between the group A in one of the pair, and group B in the other. These distances would be assumed to be randomly distributed, and a certain fraction $N_{>E_i}/N_0$ of the molecular pairs would be at or above a critical energy E_i , necessary for reaction between A and B. The fraction of molecules that have this given energy E_i , is given by the Boltzmann distribution (Moelwyn–Hughes, 1961):

$$N_i N = [\exp(-E_i/RT)] / \left[\sum_{k=0}^{k=\infty} [\exp(-E_k/RT)] \right] \quad (14.1)$$

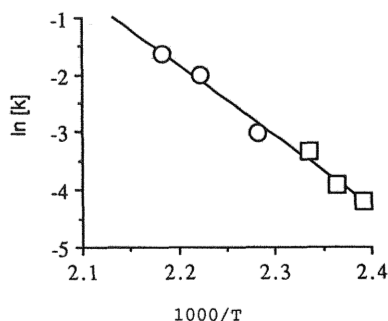


Fig. 14.3 Arrhenius plot of indomethacin decomposition: Squares are amorphous solid and circles are melt. Circles, 165°C (rate constant 0.05 h^{-1}); squares, 175°C (rate constant 0.13 h^{-1}); triangles, 185°C (rate constant 0.19 h^{-1}). (Data from Carstensen and Morris, 1993.)

where N is the total number of molecules and where the summation is overall energy levels. The fraction of molecules having energies in excess of $E_{>i}$ is then $N_{>i}/N$, given by

$$N_{>i}/N = \sum_{k=i}^{k=\infty} [\exp(-E_k/RT)] / \left[\sum_{k=0}^{k=\infty} [\exp(-E_k/RT)] \right] \quad (14.2)$$

There are several ways of approaching these summations (e.g., by considering the energy differences small and integrating). Another, discrete approach is to assume that the energy difference ΔE between adjoining energy states is constant. Here, Eq. (14.2) may be written:

$$\begin{aligned} N_{>i}/N &= [e^{-E_i/RT} + e^{-(E_i+\Delta E)/RT} + \dots] / [e^{-E_0/RT} + e^{-(E_0+\Delta E)/RT} + \dots] \\ &= \{e^{-E_i/RT} [1 + e^{-\Delta E/RT} + e^{-2\Delta E/RT} + \dots]\} / \{e^{-E_0/RT} [1 + e^{-\Delta E/RT} + e^{-2\Delta E/RT} + \dots]\} \end{aligned} \quad (14.3)$$

that is,

$$N_{>i}/N = e^{-E_i/RT} / e^{-E_0/RT} = e^{-(E_i-E_0)/RT} \quad (14.4)$$

Alternatively, if the difference between energy levels is large compared with the ground-state energy, one may simply approximate the series in the numerator and denominator of these equations with their leading terms. This leads to the same result:

$$N_{>i}/N = \sum [\exp(-E_i/RT)] / \sum [\exp(-E_0/RT)] = \exp[-(E_i - E_0)/RT] \quad (14.5)$$

If, in a time element dt , a fraction of the molecules (dN/N) reaching E_i (or higher) react, then, denoting this fraction q

$$(1/N)dN/dt = q[N_{>i}/N] = q \exp[(E_i E_0)/RT] = k_1 \quad (14.6)$$

where k_1 (by definition in differential form) is a first-order rate constant; that is, by integrating Eq. (14.6) and imposing $N = N_0$ at time $t = 0$

$$\ln[N/N_0] = -k_1 t \quad (14.7)$$

that is, first order, where the rate constant is given by

$$k_1 = q \exp[-(E_i E_0)/RT] \quad (14.8)$$

or its logarithmic equivalent:

$$\ln[k_1] = \ln[q] - E_a/RT \quad (14.9)$$

that is, an Arrhenius equation where the activation energy is given by

$$E_a = (E_i - E_0) \quad (14.10)$$

The data in Fig. 14.2 demonstrate the correctness of Eq. (14.7) (i.e., the expectancy of a first-order decomposition), and Fig. 14.3 demonstrates the correctness of Eq. (14.8).

There have been proposals (Moelwyn-Hughes, 1961; Franks, 1989) that the stability of a compound near its T_g is best described in terms of the Williams-Landel-Ferry (WLF) equation (Williams et al., 1955):

$$\ln[R] = \ln[R_g] + [C_1\{T - T_g\}/\{C_2 + (T - T_g)\}] \quad (14.11)$$

where C_2 and C_1 are constants. It is far from certain that this equation would apply to chemical reactions, but Fig. 14.4 shows its application to the data in Fig. 14.3. Several different values of C and T_g will give reasonable fits, as seen. It would seem intuitive that if the Arrhenius equation fits, then there would be values of C_2 that would make the WLF equation fit as well.

Schmitt et al. (1999) described the crystallization of amorphous lactose above the temperature of glass transition to follow the Johnson–Mehl–Avrami (Johnson and Mehl, 1939; Avrami, 1939) equations:

$$[-\ln(1 - x)]^{1/n} - k(t - t_i) \quad (14.12)$$

where x is amount decomposed, n is an integer between 1 and 4, k is a rate constant and t_i is a lag time.

Pikal et al. (1977) employed solution calorimetry to determine the amorphous content of cephalothin sodium, cefazolin sodium, cefamandole nafate, and cefamandole sodium. Because the amorphous forms are more energetic, they have a higher heat of solution, and the percentage of amorphate may be obtained, if the heat of solution of amorphate and crystalline forms separately is known.

Lo (1976) showed that ampicillin trihydrate dehydrated to amorphous ampicillin that had much poorer stability than the trihydrate. On storage the decomposition appears biphasic.

14.2. TOPOCHEMICAL REACTIONS

There are theories, akin to the foregoing, that simply, empirically state that a decomposition starts at the surface of the solid and works inward. This may be visualized as two-dimensional (the cylinder in Fig. 14.5) or as three-dimensional (as demonstrated in the sphere in Fig. 14.5).

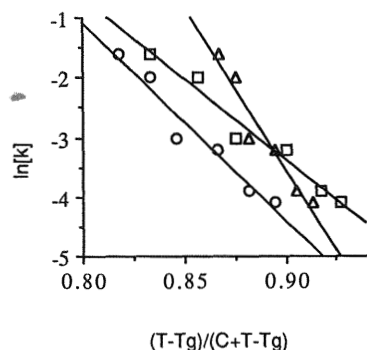


Fig. 14.4 Possible dependencies of $\ln[k]$ in Figs. 14.2 and 14.3 as a function of assumed of glass transition temperature, plotted by the inverse function of the WLF equation. Triangles: $T_g = 80^\circ$, $C_2 = 10$: $\ln[k] = 25.40 - 33.117\{T - T_g\}/\{C + (T - T_g)\}$ $R = 0.977$; Circles: $T_g = 100^\circ$, $C_2 = 6$: $\ln[k] = 45.48 - 54.47\{T - T_g\}/\{C + (T - T_g)\}$ $R = 0.97$; Squares: $T_g = 120^\circ$, $C_2 = 5$: $\{T - T_g\}/\{C + (T - T_g)\} = 0.771 \ln[k] + 0.0289$ $R = 0.982$. (Data from Carstensen and Morris, 1993.)

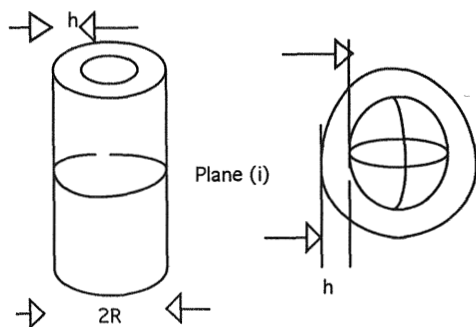


Fig. 14.5 Examples of topochemical reactions.

For a cylinder of radius R , the decomposition will work inward in a zero-order fashion (i.e., a layer h will have decomposed at time t) and

$$h = k_2 t \quad (14.13)$$

The amount remaining undecomposed at time t , therefore, would be

$$m = H\pi(R - h)^2 = H\pi(R - k_2 t)^2 \quad (14.14)$$

where H is the height of the cylinder. Because the original volume is $H2\pi(R)^2$ the retained fraction $(1 - x)$ is

$$(1 - x) = H2\pi(R - k_2 t)^2 / \{H2\pi(R)^2\} = (1 - [k_2 t / R])^2 \quad (14.15)$$

For three-dimensional, directional diffusion, the solid can be visualized as a cube originally with side a_0 cm, so that after a given time the side length a , would be

$$a = a_0 - kt \quad (14.16)$$

That is, it is assumed that the decomposition “front” progresses in a linear fashion. This is akin to physical phenomena such as crystal growth (the so-called McCabe law). At time t , therefore, there will be an amount undecomposed given by

$$N\rho a^3 = N\rho[a_0 - kt]^3 \quad (14.17)$$

where N is the number of particles in the sample and ρ is the density of the solid. The original volume of the solid was $N a_0^3$ so that the fraction not decomposed $(1 - x)$, would be given by

$$1 - x = N\rho a^3 / [N\rho a_0^3] = [a/a_0]^3 = [1 - (k/a_0)t]^3 \quad (14.18)$$

It is noted from Eq. (14.18) that the rate constant (k/a_0) is particle-size dependent.

An example of this type of decomposition pattern is aspirin in an alkaline environment (Nelson et al., 1975). This is shown in Fig. 14.6.

In general it is not possible to distinguish between a reaction of the type described by Eq. (14.18) and a first-order reaction. *It is difficult to distinguish between reaction orders in the solid state on purely statistical grounds, and other information must be available before a mechanistic model can be assigned.* Only with excellent precision, and with a fairly large number of assays and a sufficiently large decomposition, will it be possible to distinguish between the two.

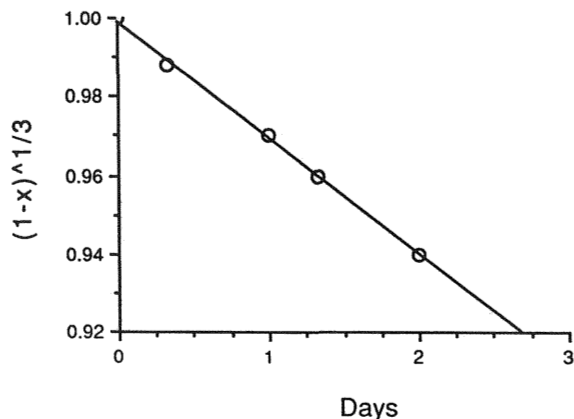


Fig. 14.6 Aspirin decomposition in a solid, alkaline environment. (Data from Nelson et al., 1975.)

14.3. THE AVRAMI-EROFEYEV EQUATIONS

Decomposition is most often associated with active sites that start as nuclei. Jacobs and Tompkins (1955) have summarized the Avrami-Erofev equations as follows:

When the nucleation is according to an exponential law; that is, when the number of nuclei follow

$$dN/dt = N_0 e^{-k_1 t} \quad (14.19)$$

where N_0 is the original number of nuclei at the temperature to which the solid has been brought from a low temperature, and if this is followed by rapid two-dimensional growth, then

$$(1 - x) = F e^{-kt} \quad (14.20)$$

F , k_1 , and k here are constants. Such a model would require a first-order decay. This rarely occurs, although some instances have been reported in literature. Shefter and Kmack (1967) studied the dehydration of theophylline hydrate and found it to follow a first-order pattern. Shefter et al. (1974) have shown first-order decomposition to occur for the dehydration of ampicillin trihydrate. In Bawn kinetics, to be covered later, the decomposition in the solid phase of the decomposition, is first order, and Pothisiri and Carstensen (1974) have shown this to be true also for *p*-aminosalicylic acid.

In many situations the nuclei will grow and then overlap, and when there is ingestion of nucleation sites and the growth nuclei can overlap, then, the Avrami-Erofev equation takes the form

$$-\ln[1 - x] = Q\{e^{-k_1 t} - 1 + k_1 t - [(k_1 t)^2/2!] + [(k_1 t)^3/3!]\} \quad (14.21)$$

If the lag time is denoted t_l , then in the decay period ($t \gg t_l$) this reduces to

$$-\ln[1 - x] = kt^3 \quad (14.22)$$

which is one common form of the Avrami equation.

The program in Table 14.1 and the printout in Table 14.2 demonstrates the danger in simply applying Eq. (14.22) to decomposition data. The program calculates a series of data according to Eq (14.21) and the tabulation (see Table 14.2) gives the possibility of graphing according to Eq. (14.21) (Fig. 14.7), and Eq. (14.22) (Fig. 14.8).

The previous sections have dealt with decompositions that occur randomly in a space or on a surface. The section to follow will deal with the situation in which decomposition is tied to particular sites that are created as a function of time. This type of reaction has been assigned quite frequently in recent literature, in particular, to pseudopolymorphic transformations and dehydration kinetics of hydrates.

In the hydrate water molecules form part of the matrix. Dehydration kinetics of hydrates has had the attention of the pharmaceutical scientist for some time. Byrn (1982) has developed a generalized kinetic theory for isothermal reaction in solids, and theophylline has been used as a model for several studies of this kind (Lin and Byrn, 1979; Suzuki et al., 1989; Agbada and York, 1994).

The Avrami–Erofeyev model used for this type of kinetics (Avrami, 1939) will be dealt with in the following in a somewhat simplified manner. The model assumes that volumes within the solid at a given time t are activated, and that decomposition may occur in these areas and not in the areas that at time t still remain “nonnu-

Table 14.1 Program for Eqs. (14.21) and (14.22)

```
100 FOR T = 0 TO 1.5 STEP .1
110 X1 = EXP(-T)
120 X2 = (T^2)/2
130 X3 = (T^3)/3
140 Y1 = X1-1+T+X2-X3
150 Y2 = 1-Y1
160 Y3 = -LOG(Y2)
170 Z = T^3
150 PRINT T,Y1,Y3,Z
160 NEXT T
```

Table 14.2 Decomposition Data According to Eqs. (14. 21) and (14.22)

Time, kt	x	$-\ln(-x)$	$(kt)^3$
0	0	0	0
0.1	0.00950	0.0955	0.001
0.2	0.0362	0.036	0.080
0.3	0.077	0.080	0.027
0.4	0.129	0.211	0.064
0.5	0.327	0.396	0.216
0.6	0.399	0.509	0.512

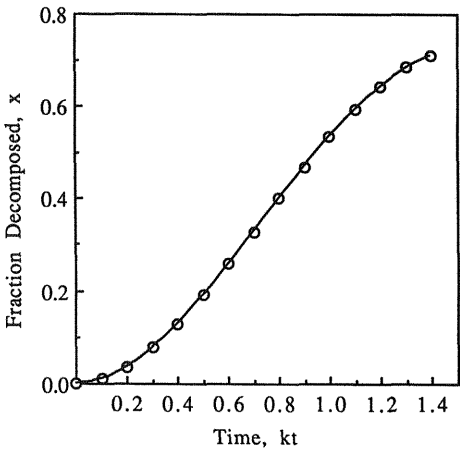


Fig. 14.7 Decomposition data in Table 14.2 plotted according to Eq. (14.21).

cleated.” This may occur in strings (one-dimensional diffusion), areas (two-dimensional diffusion), and volumes (three-dimensional diffusion). The approximate mathematical development follows the same path in the different cases, and only the latter will be derived.

For simplicity it is assumed, in Fig. 14.9, that only the volume cornered by A is nucleated and the rest of the solid is not. This could equally well have been scattered volumes of a total volume equal to the condensed volume shown in Fig. 14.9, and the result, therefore, will be the same, except that, in the scattered case, the volumes may “grow together.” This is not considered in the model (but will be considered in the Prout–Tompkins model).

If the nucleation occurs zero order in each direction, then the side of the nucleated cube, at time t , is kt , so that the number of nuclei, N_3 , at time t is

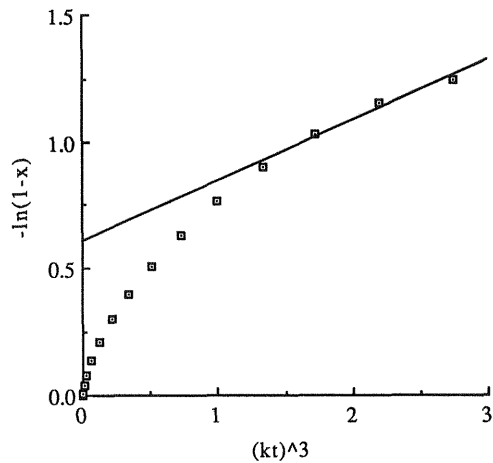


Fig. 14.8 Decomposition data in Table 14.2 plotted according to Eq. (14.22).

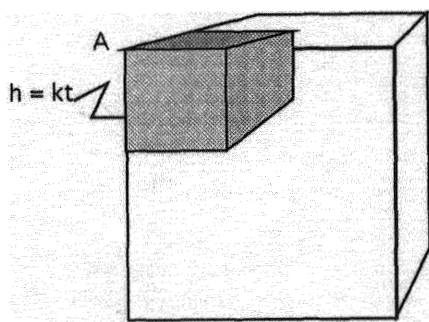


Fig. 14.9 Schematic for approximate Avrami–Ereyefov model.

$$N_3 = (k_1 t)^3 \quad (14.23)$$

If the nucleation occurs in a plane, then (two-dimensional case)

$$N_2 = (kt)^2 \quad (14.24)$$

and if it occurs along a line (a string), then (one-dimensional case)

$$N_1 = (kt) \quad (14.25)$$

Figure 14.9 applies to the three-dimensional case, and the decomposition is assumed to be (a) in line with first-order kinetics proportional to the concentration of unreacted solid in the nucleated volume; (b) proportional to the number of nuclei and, hence, in view of Eq. (14.23) proportional to $(kt)^3$; and (c) not occurring at all in the nonnucleated volume. This reasoning leads to

$$d(1-x)/dt = -q(1-x)(kt)^3 \quad (14.26a)$$

in the three-dimensional case, and in general to

$$d(1-x)/dt = -q(1-x)(kt)^n \quad (14.26b)$$

n being unity, two or three, depending on the dimension. Equation (14.26b) may be rewritten:

$$d \ln[1-x] = -qk^n t^n \quad (14.27)$$

which integrates to

$$\ln[1-x] = -[qk^n/(n+1)]\{(t^{(n+1)})\} = -\exp(Q_1)t^{(n+1)} \quad (14.28)$$

in line with the expected linearity in Fig. 14.8. $Q_1 = [qk^n/(n+1)]$, here is a constant. Taking logarithms of Eq. (14.28) now gives

$$\ln\{-\ln(1-x)\} = Q_1 + (n+1)\ln[t] \quad (14.29)$$

which is the conventional plotting mode, as employed by Dudu et al. (1995). These authors used microcalorimetric methods and showed the dehydration of theophylline hydrate to be a two-step process obeying the equation

$$[-\ln(1-x)]^{0.25} = kt \quad (14.30)$$

which is a variant of Eq. (14.28), with $n = 3$. Hence, in their case, the process is a three-dimensional, diffusional process.

14.4. NUCLEATION FOLLOWED BY FAST KINETICS (POLYMORPHIC TRANSFORMATIONS)

Polymorphic transformation rates have lately become of importance; an example is a recent article by York et al. (1994), dealing with the dehydration kinetics of theophylline. The article by Ng (1972) is similarly instructive in the sense that it reviews all the equations that have been developed for polymorphic transformation kinetics.

Usually the transformation kinetics are S-shaped curves, and before any model is imposed on the data, the following model should be considered. (This is comparable with the model proposed by Carstensen and Van Scoik, 1990): If the phenomenon that governs the transformation is essentially the nucleation lag time, then the curves may be considered as representing either a normal or a lognormal error curve and the mean would be the mean (or geometric mean) nucleation time. What this states is that each particle, in a sense, acts as its own entity, that there is a nucleation time (with an error or a variance attached to it), and the particle will endure the nucleation time, and then decompose, individually, very rapidly.

The reason for the lognormal relation is not difficult to rationalize. Solids are usually lognormally distributed. If the nucleation time is inversely proportional to size, then it, too, would be lognormally distributed.

To judge whether such a relation pertains, the fraction decomposed is, therefore, converted to a cumulative Z -value (by means of a normal error table), and this is plotted versus either t or $\ln[t]$, to yield a straight line:

$$Z = k \ln[t] - Q_1 \quad \text{or} \quad kt - Q_2 \quad (14.31)$$

$Z = 0$ corresponds to the average nucleation time, t_{avg} , that is

$$t_{\text{avg}} = \exp\{Q_1/k\} \quad \text{or} \quad t_{\text{avg}} = Q_2/k \quad (14.32)$$

and the Q -values would correspond to the standard deviation of the nucleation time.

Dehydration, at times, results in a morphic transformation. For instance, Lo (1976) showed that the transformation of crystalline ampicillin trihydrate to amorphous penicillin was primarily first-order and either was first-order or followed a contracting cylinder model $[(1-x)^{1/2}]$ being proportional to time].

14.5. SURFACE NUCLEATION (PROUT-TOMPKINS MODEL)

If a solid is placed in a vacuum and exposed to temperatures at which it decomposes at a measurable rate, one of the following situations may arise:

- I Solid $\rightarrow$ solid + solid
- II Solid $\rightarrow$ solid + liquid
- III Solid $\rightarrow$ liquid + liquid
- IV Solid $\rightarrow$ solid + gas
- V Solid $\rightarrow$ liquid + gas
- VI Solid $\rightarrow$ gas + gas

Other schemes are theoretically possible, but not likely. Of the foregoing, it is schemes IV and V that will be treated in some detail in the following, because they are the ones most investigated in the pharmaceutical sciences. It will later be

shown that most pharmaceutical systems will not be of such a “purist” nature, but the experiences gathered from examining them will throw light on several important, real-life situations.

14.5.1. The Solid to Solid-plus-Gas Reaction

Not all S-shaped curves will neatly fit topochemical or Avrami equations. The data in Table 14.3 represent an S-shaped curve and were obtained by a reaction that produced a solid and a gas, and if plotted by Eq. (14.29) then Fig. 14.10 results.

The plot may, at first glance, seem fairly linear, but the point is that there is a *trend*, in that the deviations from the line are (+) (part AB), (–) in part BC, and then again (+) in part CD. It is visually obvious, as well, that the curve is still S-shaped. Such curves also fail to give an integer (2, 3, or 4) as dictated by the model.

The solid $\rightarrow$ solid + gas type of reaction has been investigated by Prout and Tompkins (1944), who used potassium permanganate as a model substance. Pharmaceutical solids have been tested later [e.g., *p*-aminosalicylic acid was investigated by Kornblum and Sciarrone (1964) and by Carstensen and Pothisiri (1975)]. A typical example of such a reaction is shown in Table 14.3 and the readers may satisfy themselves by plotting x versus t , that the plot is, indeed S-shaped.

No solid has a smooth surface (i.e., there are always surface imperfections). These could be “steps” in the surface or they could be crystal defects. These sites are more energetic than the remaining sites. They are most likely to occur at surfaces, which, in any event, are populated with molecules that are unlike the molecules in the bulk of the crystal. For instance they have at least one less neighbor than bulk molecules. It is assumed that decomposition is more likely to occur at such “activated” sites (Fig. 14.11).

Once a molecule decomposes at an activated site it changes its geometry; hence, the neighboring molecules are more likely to decompose. There will then be a chain or plane of activated molecules forming, with a probability of α (see second figure in Fig. 14.11). The rate α , of formation of activated molecules, N in number at time t , is dN/dt , and this is proportional to N . Initially this is then given by

$$[dN/dt]_0 = \alpha[N + N_0] \quad (14.33)$$

Table 14.3 Decomposition Data of 4.6 mol of a Solid Following the Prout–Tompkins Model

Time (t)	Gas (mmol)/ 4.6 mmol solid	Mole fraction x decomposed	$\ln\{x/(1 - x)\}$
0	0		
1	0.08	0.017	–4.034
2	0.46	0.1	–2.197
3	1.16	0.252	1.087
4	2.37	0.515	0.061
4.5	3.20	0.696	0.827
5	3.76	0.817	1.499
6	4.15	0.902	2.222

$$y = -4.1317 + 2.7981x \quad R^2 = 0.995$$

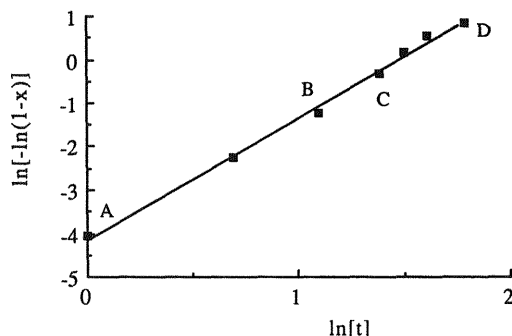


Fig. 14.10 Data in Table 14.3 treated according to Eq. (14.29).

It is obvious that after even a short period of time N becomes much larger than N_0 , so that this latter can be dropped at times even remotely larger than zero.

After a certain while (see last inset in Fig. 14.11), planes will start to merge, and hence there will be a termination probability β , so that at measurable times, Eq. (14.33) becomes

$$dN/dt = \{\alpha - \beta\}N \quad (14.33)$$

Both α and β are functions of t (or what is equivalent, to the fraction decomposed x). It is reasonable to assume that

$$a = b \quad \text{at} \quad t = t_{1/2} \quad (\text{or } x = 0.5) \quad (14.34)$$

that is, at the time point at which one-half of the substance has decomposed. Also,

$$\beta = 0 \quad \text{at} \quad t = 0 \quad (\text{or } x = 0) \quad (14.35)$$

for there can be no termination probability at time zero. One (not necessarily the correct) function which satisfies this condition is

$$\beta = 2x\alpha \quad (14.36)$$

When this is inserted in Eq. (14.33) one obtains

$$dN/dt = \alpha[1 - 2x]N \quad (14.37)$$

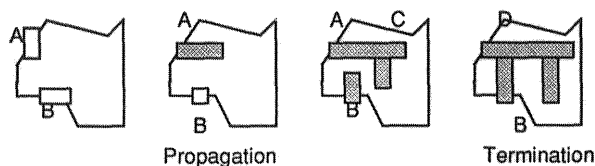


Fig. 14.11 Schematic of model leading to Prout-Tompkins kinetics: A and B are active surface sites. Propagation of A proceeds AC (third inset), as propagation at B starts. Branching then occurs at C, and finally there is termination of one (or the other) of the branches.

The decomposition rate dx/dt is proportional to N ; i.e., $dx/dt = kN$ or

$$N = (1/k)\{dx/dt\} \tag{14.38}$$

Equation (14.37) can now be written

$$dN/dt = (\alpha/k)[1 - 2x] dx/dt \tag{14.39}$$

Chain differentiation of dN/dt gives

$$dN/dt = [dN/dx][dx/dt] \tag{14.40}$$

Introducing Eq. (14.39) into Eq. (14.40) gives

$$dN/dt = [dN/dx][dx/dt] = (\alpha/k)[1 - 2x]dx/dt \tag{14.41}$$

dx/dt is canceled out of the last part of this equation to give

$$dN/dx = \{\alpha[1 - 2x]/k\} \tag{14.42}$$

which integrates to

$$N = (\alpha/k)(x - x^2) \tag{14.43}$$

Since, by (Eq. 14.38), $N = (1/k)\{dx/dt\}$, it follows from Eq. (14.43) that

$$(1/k) dx/dt = (\alpha/k)x(1 - x) \tag{14.44}$$

which integrates to

$$\ln[x/(1 - x)] = \alpha(t - t_{1/2}) \tag{14.45}$$

The equations have a zero time problem, because the equation is not defined for $x = 0$. This is a consequence of neglecting N_0 . Similar paradoxes exist in the scientific literature. The Gibbs adsorption isotherm, for instance, is not defined for concentration, $C = 0$ (i.e., for a liquid without surfactant). In solid-state stability, it might be thought of in the vein, that as the material is being produced (i.e., at time zero; e.g., through recrystallization), it is already decomposing (however little).

Data are plotted according to Eq. (14.35) in Fig. 14.12, and the linearity is good. There are several other aspects that may convince a scientist that this is the type of reaction at hand. First of all, Arrhenius plotting is good, and *the activation energy is usually three to four times as high as in that of other reactions in the solid*

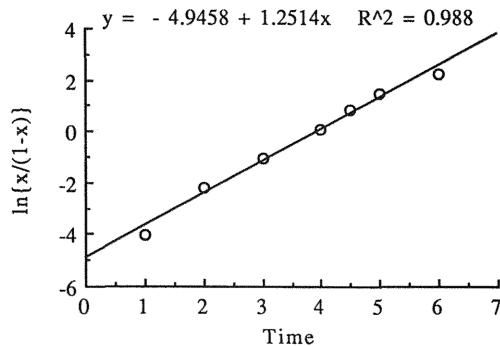


Fig. 14.12 Data from Table 14.3.

(and liquid) state. The reason for this is that the rate-determining parameter in Eq. (14.45) is α (i.e., it is actually a propagation probability that is measured, not a rate constant in the usual sense). Whenever a compound “melts with decomposition,” then there is a good possibility that the “melting range” depicts the interval in which the reaction occurs with a measurable rate, that it is too slow below this range, and too fast above the range, and in such a circumstance the activation energy is high, and a Prout–Tompkins reaction may most likely be applicable.

A note on the half-life is in order. There is frequently a substantial lag time involved in this (and other solid) type reactions. Because many are carried out under vacuum (e.g., when break-seal tubes are used, or when manometers are glass-blown directly unto the reaction vessel), and heat transmission, therefore, is poor, so that it will be a while before the *solid itself* actually attains the elevated temperature. An experimental remedy is to test the heat transmission by checking the length of time it takes for a stable solid substance with known melting point and heat capacity to melt at that temperature, and to do this with three substances (benzoic acid being one), and construct a calibration curve. If it is then calculated that at a given test temperature, T K, it takes t minutes for the solid to attain the given temperature, then the average time may be obtained by the integral mean value theorem. Half of this time can then be subtracted from the time points used.

For Prout–Tompkins plotting, this does not apply, but it may be a source of error in Avrami plotting.

The solid $\rightarrow$ solid-plus-gas reaction embodies the dehydration of solid hydrates. Leung et al. (1998a,b) have shown that aspartame 2.5 hydrate cyclizes by Prout–Tompkins kinetics and that the rate constants follow an Arrhenius equation.

14.5.2. Temperature Dependence of the Solid to Solid-Plus-Gas Reaction

It should be pointed out, that the solid to solid-plus-gas reaction may be so only over a certain temperature range, or to a certain degree of decomposition. Figure 14.13 shows the eutectic diagram of a compound A with its solid decomposition product B. If the study is carried out at temperatures below the eutectic temperature T^* , then the reaction will be solid to solid-plus-gas. If above the eutectic temperature, then the reaction will be solid to solid plus liquid plus gas. (If above the highest melting point, then it will be liquid kinetics.) The compounds reported in literature to be of the solid to solid-plus-gas type are most often inorganic salts [e.g., potassium permanganate (Prout and Tompkins, 1944); silver permanganate (Goldstein and Flanagan, 1964)], and some organic compounds, such as oxalic acid, *p*-aminosalicylic acid (Kornblum and Sciarrone, 1964; Pothisiri, 1975a,b), or indomethacin (Carstensen and Morris, 1995).

Olsen et al. (1997) showed cefaclor monohydrate to decompose (as judged by related substances) by first-order kinetics. The rate constants could be plotted by Arrhenius plotting and were consistent with ambient rate constants. The reaction scheme, when amorphous material was present, was such that the rates were faster at early time points and then becoming equal to those of the crystalline modification. The conclusion was that the initial phase was decomposition of amorphous content parallel to conversion of amorphous to crystalline drug.

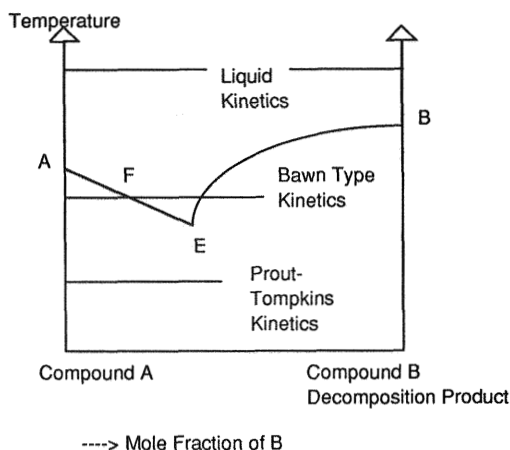


Fig. 14.13 Eutectic diagram of a compound and its decomposition product: At temperatures higher than the melting point of B only liquid kinetics would be expected. At temperatures lower than the eutectic point only solid state kinetics (e.g., Prout–Tompkins kinetics) would be expected. In intermediate temperatures, so-called Bawn kinetics apply.

At times the solid-state reaction cannot be completely specified, yet may be described in analytical terms. Tzannis and Prestrelski (1999) described the effect of sucrose on the stability of trypsinogen, during spray-drying, by plotting denaturation temperatures as a function of melting temperature and found a linear increase between residual activity after spray-drying, and melting temperature. Adler and Lee (1999) have reported on the stability of lactate dehydrogenase in spray-dried trehalose.

14.6. THE NG EQUATION

There are a multitude of “types” of S-shaped curves, and one, somewhat distorted, shape is as shown in Fig. 14.14. Ng (1975) suggested the following global, empirical equation for this and other types of solid-state decomposition:

$$dx/dt = kx^n(1-x)^p \quad (14.46)$$

If both n and p are unity, then the equation becomes the Prout–Tompkins equation. A set of data illustrating this is shown in Table 14.4. These are the data on which Fig. 14.14 is based.

In the first two columns of the table the time required for decompositions of 0, 0.1, 0.2, ..., have been determined. (Data treatment is actually easier if random times are used, with the associated fractions decomposed.)

The average decompositions at interval midpoints are then determined (columns 3 and 4), and the value of dx/dt is then calculated (as shown in the table footnote). The Ng equation may be expressed in logarithmic form.

$$\ln[dx/dt] = n \ln[x] + p \ln[1-x] + \ln[k] \quad (14.47)$$

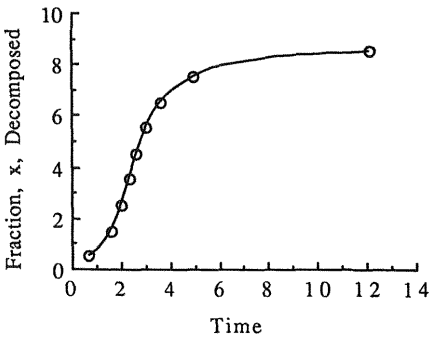


Fig. 14.14 S-shaped curve following the Ng equation: data in Table 14.4.

If the data in Table 14.4 are transformed and $\ln[dx/dt]$ is multiply regressed against $\ln[x]$ and $\ln[1 - x]$, then values of $n = 2$ and $p = 3$ are obtained.

14.7. THE SOLID TO LIQUID-PLUS-GAS REACTION

Many more compounds seem to decompose by this reaction scheme than by the solid to solid-plus-gas one. As mentioned in the caption to Fig. 14.13, this type of reaction

Table 14.4 Example of Data Amenable to Treatment by the Ng Equation

Time	Fraction <i>x</i> decomposed	Average time, <i>t</i>	Average fraction, <i>x</i> decomposed	<i>dx/dt</i> (from curve)
0	0			
		0.686	0.05	0.0729
1.371	0.1	1.615	0.15	0.2048 ^a
1.859	0.2	2.021	0.25	0.3087
2.183	0.3	2.328	0.35	0.3450
2.472	0.4	3.632	0.45	0.3125
2.792	0.5	3.009	0.55	0.2304
3.226	0.6	3.604	0.65	0.1323
3.982	0.7	4.959	0.75	0.0512
5.935	0.8	12.107	0.85	0.0810
18.280	0.9			

^aObtained by: $0.1/(1.859-1.371) = 0.1/0.488 = 0.2048$

kinetics is usually referred to as Bawn kinetics (Bawn, 1955). The situation at time t is as shown in Fig. 14.15 and, as seen, there will be a certain amount of liquid decomposition product. This amount corresponds to the amount of drug decomposed. However, the liquid decomposition product will dissolve parent compound to the extent, S (mole drug per mole decomposition product), to which it is soluble, so that the amount present in the solid state at time t is the original number of moles A_0 , minus the amount decomposed A_0x , minus the amount dissolved, A_0Sx .

The rate of decomposition would be the sum of the rates of decomposition in the solid state (assumed first order with rate constant k_s , time^{-1}) and in the dissolved state (assumed first order with rate constant k_1 , time^{-1}). The rate equation is hence

$$dA/dt = -k_s[A_0(1-x) - A_0xS] - k_1[A_0xS] \quad (14.48)$$

Noting that

$$A/A_0 = (1-x) \quad (14.49)$$

it follows, by division through by A_0 that

$$d(1-x)/dt = -k_s[1-x-xS] - k_1xS \quad (14.50)$$

or, noting that $d(1-x) = -dx$

$$dx/dt = k_s[1-x-xS] + k_1xS = k_s[1+Bx] \quad (14.51)$$

where

$$B = [(k_1/k_s) - 1]S - 1 \quad (14.52)$$

Equation (14.51) may be integrated, and yields

$$\ln[1 + \{Bx\}] = Bk_st \quad (14.53)$$

Using B as an adjustable parameter, it is possible to find the value that makes the data profile through the origin, as dictated by Eq. (14.53), and also gives the best fit.

Figure 14.16 and Table 14.5 show an example of data from decomposition of *p*-methylaminobenzoic acid.

To plot this according to Eq. (14.53) it is necessary to assume values of B , plot the data, and assess the goodness of fit by some criterion. A different value of B is then chosen, and this process repeated until a "best" value of B is arrived at. It is possible to show that in general the sums of the squares of the deviations

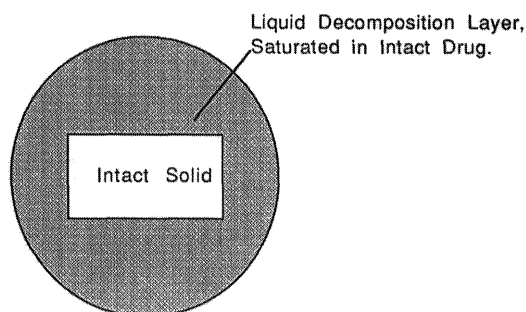


Fig. 14.15 Situation leading to Bawn kinetics.

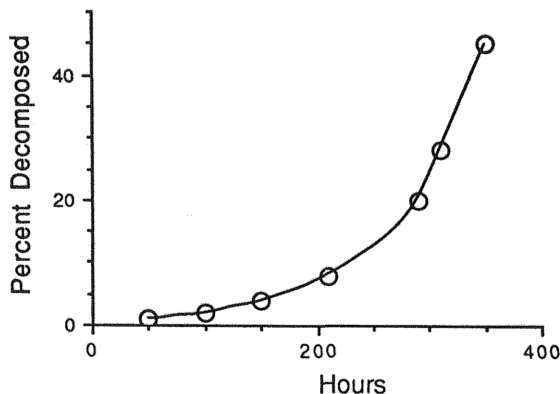


Fig. 14.16 Data from Table 14.5: Decomposition of *p*-methylaminobenzoic acid. (Data from Carstensen and Musa, 1972.)

($s_{yx}^2 = \sum (y - \bar{y})^2 / (n - 2)$) of the points from the ensuing line is used as a criterion. A different criterion is the correlation coefficient. Frequently, this is also not a good criterion, and criteria for linearity (e.g., Durbin–Watson statistics) are the best. For data fitting to Eq. (14.53) the line must pass through the origin. Fitting the data in this fashion is shown in Table 14.6 for three values of B (0.1, 0.85, and 2.0). It is best to do this by computer, and a simple program in BASIC is shown in Table 14.7.

The number of data points are inserted, the assumed value of B is inserted and the program run. One can then in three or four tries arrive at a “best” value for B ($= 0.85$).

In Eq. (14.53), using the correlation coefficient is not a good parameter, because it simply increases with increasing values of B up to a very high (unrealistic) value, also resulting in a very high intercept. All the correlation coefficients are good. The best criterion would be a criterion that dealt with curvature, but a simpler one, as stated, is simply to note the intercept, which should be zero.

Studies of this type are usually performed on a vacuum rack. In this, the pressure is monitored as a function of time, and the sample can be observed. At a given time point (which is quite reproducible), the last trace of solid will disappear (Fig. 14.18). At this time point, t^* , the amount not decomposed, $A_0(1 - x)$, is just sufficient to dissolve the amount of liquid A_0x , present at time t^* .

$$S = (1 - x^*)/x^* \quad (14.54)$$

where x^* is the mole fraction decomposed at time t^* . Therefore, Eq. (14.53) is valid from time zero to time t^* . If $t^* = 350$ (as in the example used here), and $x^* = 0.45$ at this point, it follows that

$$S = 0.55/0.45 = 1.22 \text{ mol/mol} \quad (14.55)$$

Table 14.5 Decomposition Data for *p*-Methylaminobenzoic Acid

Time (h)	0	50	110	150	210	290	310	350
% Decomposed	0	1	2	4	8	20.5	27.9	45

Table 14.6 Data in Table 14.5 Treated by Eq. (14.53)

Time (h)	$\ln[1 + Bx]$		
	$B = 0.1$	$B = 0.85$	$B = 2$
50	0.095	0.615	1.099
100	0.182	0.993	1.610
150	0.334	1.481	2.200
210	0.588	2.054	2.830
290	1.099	2.890	3.710
310	1.335	3.210	4.040
350	1.705	3.677	4.510

Table 14.7 Program for Obtaining Best Values by Manual Iteration

```
100 PRINT "Type in data as x,y, in 400 block"
110 INPUT "Number of Data Points=";N1
120 INPUT "Iteration Parameter, B=";B
130 PRINT "T";SPC(6);"X";SPC (6);"LN(1 + BX)
140 PRINT "_____ "
200 READ A,C
210 X = A
220 Y = LOG(1 + B*C)
230 X1 = X1 + X
240 X2 = X2 + (X^2)
250 Y1 = Y1 + Y
260 Y2 = Y2 + (Y^2)
270 Z1 = Z1 + (X*Y)
280 N2 = N2 + 1
300 PRINT X;SPC(6);C;SPC(6);Y
310 IF N2 = N1 goto 700
400 DATA 50,1
410 DATA 100,2
420 DATA 150,4
430 DATA 210,8
440 DATA 290,20
450 DATA 310,28
460 DATA 350,45
700 Z2 = X2 - ((X1^2)/N2)
710 Z3 = Y2 - ((Y1^2)/N2)
720 Z4 = Z1 - (X1*Y1/N2)
730 Z5 = Z4/Z2
740 Z6 = (Y1-(Z5*X1))/N2
750 PRINT
760 PRINT "Slope=";Z5
770 PRINT "Intercept="; Z6
780 Z7 = (Z4^2)/(Z3*Z2)
790 Z8 = (Z7)^(0.5)
800 PRINT "Correlation Coefficient =" ;Z8
810 Z9 = (Z3 - ((Z5^2)*Z2))/(N2-2)
820 PRINT "syx^2=";Z9
```

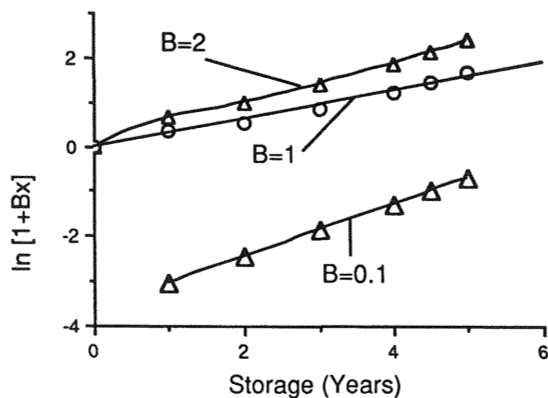


Fig. 14.17 Data from Table 14.6 treated by Eq. (14.53).

The slope in this case is 0.01 h^{-1} . Since the slope is $[Bk_s]$ it follows that

$$k_s = \text{slope}/B = 0.01/0.85 = 0.012 \text{ h}^{-1} \quad (14.56)$$

k_1 is now calculated from Eq. (14.52).

$$0.85 = [(k_1/0.012) - 1] 1.22 - 1 \quad (14.57)$$

$$\text{that is } k_1 = 0.03 \text{ h}^{-1} \quad (14.58)$$

Beyond t^* the system is a solution system, and should decompose by first-order kinetics. The density of the liquid will actually change with time, but it is assumed that both parent drug and decomposition product have approximately the same density. The Moles/cm³ density is denoted ρ and since there is a total number of A_0 mol, the volume of liquid is A_0/ρ . The initial molar concentration (at time t^*) is, therefore, $A_0(1 - x^*)/[A_0/\rho] = (1 - x^*) \cdot \rho$. The time is counted from $t = t^*$, and the concentration at time $(t - t^*)$ is $(1 - x) \cdot \rho$, so that

$$\ln[(1 - x) \cdot \rho] = k_1 t + \ln[(1 - x^*) \cdot \rho] \quad (14.59)$$

or

$$\ln[(1 - x)/(1 - x^*)] = -k_1(t - t^*) \quad (14.60)$$

or

$$x = 1 - (1 - x^*)e^{-k_1 t} \quad (14.61)$$

Data of this type, for *p*-methylaminobenzoic acid, are presented in Figs. 14.18 and 14.19. It is seen that the data are quite first order. The first order rate constant obtained from this plot is $k_1 = 0.040 \text{ h}^{-1}$ in quite good agreement with the value of 0.03 found from the first part of the curve.

It is noted that when the total curve is plotted (i.e., when Figs. 14.18 and 14.19 are combined), then an S-shaped curve results. Unlike the Prout-Tompkins curve, the Bawn curve is a two-phase curve, one part relating to the phase where there is solid present, the other to the part where all solid has dissolved.

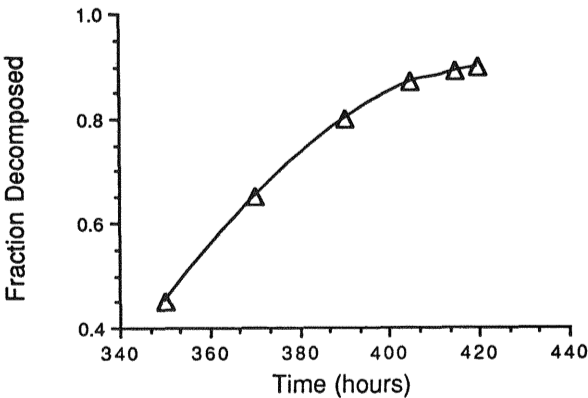


Fig. 14.18 Decomposition of *p*-methylaminobenzoic acid after t^* (350 h), at which point $x = 0.45$ i.e., $1 - x = 0.55$. (Data from Carstensen and Musa, 1972.)

The values of x^* obtained at t^* will differ from temperature to temperature because the solubility is a function of temperature. This is actually the value of the liquidus line on a eutectic diagram. The melting point depression curve (Maron and Prutton, 1958) is given by

$$\ln(1 - x^*) = (\Delta H/R)[(1/T_f) - (1/T)] \tag{14.62}$$

Such plots are quite linear, as shown in Fig. 14.20.

14.8. DIFFUSION CONTROLLED INTERACTIONS

Figure 14.21 shows a situation where an ideally shaped solid A, is in contact with another such solid B. The contact area is assumed to be 1 cm². It is assumed that A can react with B in this situation; that is,

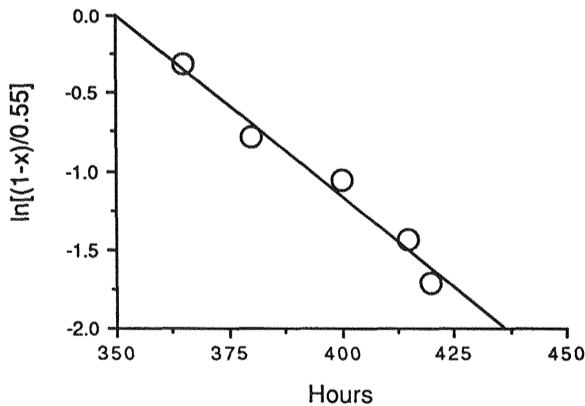


Fig. 14.19 Data in Fig. 14.18 treated according to Eq. (14.61). (Data from Carstensen and Musa, 1972.)

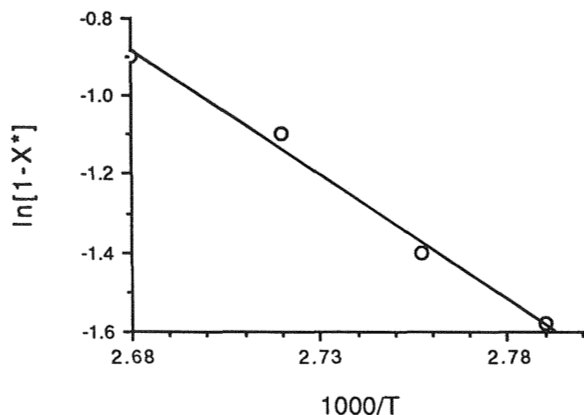


Fig. 14.20 $\ln[1 - x^*]$ as a function of $1000/T$: least-squares equation; $y = 16.19 - 6.37x$ ($R = 1.00$). (Data from Carstensen and Kothari, 1981.)

As the reaction proceeds decomposition product C will accumulate between A and B, and at a given time t , compound A must diffuse to the surface of compound B through a layer of compound C, h -cm thick, for the reaction to take place. The density of B is denoted ρ . A layer of B, h -cm thick would contain $h\rho$ g of B; hence,

$$dB/dt = \rho dh/dt \quad (14.64)$$

By Fick's first law, dB/dt is inversely proportional to h , so that we may write

$$\rho dh/dt = q/h \quad (14.65)$$

or:

$$h \cdot dh = [q/\rho]dt \quad (14.66)$$

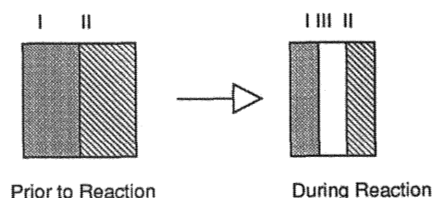


Fig. 14.21 Interaction between two solids with decomposition layer separating the two reacting species, necessitating diffusion of one of the reactants through the decomposition layer. (Data from Carstensen and Musa, 1972.)

This may be integrated to

$$h^2 = [2q/\rho]t = k't \tag{14.67}$$

or:

$$h = [k't]^{1/2} \tag{14.68}$$

where $k' = 2q/\rho$. If, as indicated in the lower line of Fig. 14.21 two compounds A and B are cubical, of side length a_0 initially, and a at time t , and if B is surrounded by A

$$h = a_0 - a \tag{14.69}$$

The amount retained at time t is

$$\begin{aligned} (1 - x) &= [a/a_0]^3 = [(a_0 - a_0 + a)/a_0]^3 \\ &= [1 - (h/a_0)]^3 = [1 - \{kt\}^{1/2}/a_0]^3 \end{aligned} \tag{14.70}$$

or

$$\{1 - (1 - x)^{1/3}\}^2 = kt/a_0^2 \tag{14.71}$$

where x is fraction decomposed. It is seen that the rate constant is related to the particle size (i.e., the finer the particles the larger the rate constant). A system of this type is, again, the aspirin–sodium bicarbonate system, but at lower temperatures. At higher temperatures, the autodecomposition of aspirin is higher than the diffusion coefficient (related to q), and the reaction at higher temperatures then follows [see Eq. (14.18)] (Nelson et al., 1974).

Recently, it has become customary to compare polymorphic and pseudopolymorphic transformation data with prevailing solid-state equations (e.g., forms of the Ng equation). Several such equations, some of them already alluded to, are listed in Table 14.8.

There has been a tendency in recent literature to simply fit data to several (or all) of these equations, and the equation that gives the “best fit” is then assumed to be the mechanism. Figure 14.23, for instance, shows a literature example of such data. It is claimed that these data best fit a Jander equation (and such treatment is shown in Fig. 14.24), but first of all the fit is not good, and second, it is obvious that the phase C in the Jander model (see Fig. 14.21) cannot possibly apply to a polymorphic transformation where the reaction is simply $A \rightarrow B$, not $A + B \rightarrow C$. *It is emphasized here that sorting out mechanisms by statistical analysis can be fallacious.*

Table 14.8 Equations Relating to Decomposition in the Solid State

$\ln(x/(1 - x)) = kt$	Surface nucleation, Prout–Tompkins equation
$\{-\ln(1 - x)\}^{1/n} = kt$	n -Dimensional nuclear growth (Avrami and Erofeyev)
	n -Dimensional nucleus growth
$1 - (1 - x)^{1/n} = kt$	n -Dimensional boundary reaction
$x^2 = kt$	Diffusion in one dimension
$(1 - x) \ln(1 - x) + x = kt$	Diffusion in two dimensions
$(1 - (1 - x)^{1/3})^2 = kt$	Diffusion in three dimensions (Jander equation)

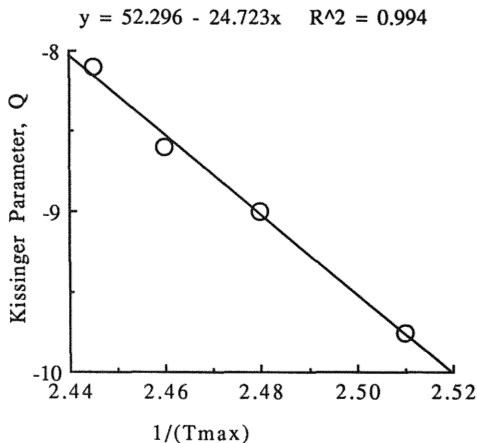


Fig. 14.22 Kissinger plot of polymorph II of glybuzole. (Data from Otsuka et al., 1999.)

Several modelistic investigations in this field have appeared in recent years. Fini et al. (1999) have studied the dehydration and rehydration of diclofenac salt hydrate at ambient temperature. Otsuka et al. (1999) investigated three forms of glybuzole (I, II, and amorphate), (Figs. 14.23 and 14.24) and found all to have fairly much the same solubility. Neither form I nor II changed after storage at 40°C at 75% and 0% RH for 2 months. DSC for form I showed no peak other than a sharp melting endotherm at 167.4°C, form II showed a slight endotherm at 116.8°C and a sharp endotherm at 166.6°C. The amorphate showed a (slight) exotherm peaking at 81.5°C, presumably owing to crystallization, and a sharp endotherm at 167.3°C. From this it would be reasonable to conclude that form II is stable at room temperature and transforms to I at 116.8°C, this latter form being stable at the higher temperatures.

The authors estimated the polymorphic stability of form II by way of the Kissinger equation (Kissinger, 1956).

$$\partial\{\ln(\phi/T_{\max}^2)/\partial(1/T_{\max})\} = -E_a/R \tag{14.72}$$

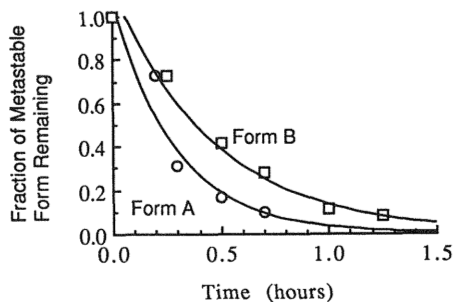


Fig. 14.23 Literature data dealing with two polymorphic transformations allegedly diffusional because it adheres (somewhat) to a Jander model.

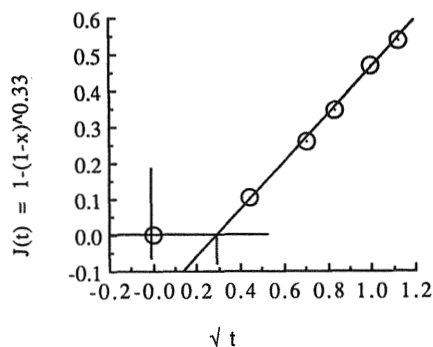


Fig. 14.24 Data from form B in Fig. 14.22 treated according to a Jander model. The curve follows the least-squares fit equation: $J(t) = -0.194 + 0.652\sqrt{t}$.

where ϕ is the rate of heating, $T_{\max}$ is the temperature at the peak maximum in the DSC, E_a is the activation energy, and R is the gas constant. If the experiment is conducted at different heating rates, different $T_{\max}$ values result, and in the case of glybuzole there were four such values.

It can be seen from their graph that the activation energy is $24.723 \times 1.99 = 49.2$ kCal/mol. Otsuka et al. (1991, 1993, 1999) employed the Jander equation to explain crystallization rates of compounds (e.g., amorphous glybuzole). However, the Jander equation is based on an assumption of a layer of “reaction product,” and such a layer (i.e., such a model) cannot be conceived of in a polymorphic transformation, because what would be the “reaction product”?

14.9. GENERAL INTERACTIONS IN DOSAGE FORMS

It is tempting to think of a tablet as an agglomeration of individual particles, independent of one another, but this cannot be true. By their mere nature, particles are fused together (by either brittle fracture or by plastic deformation in tablets or tamping in capsules), and if the created contact area is between two different components of the tablet (one being the drug), then there is the possibility of interaction. It is highly likely that moisture plays a part in all of these. In fact, in one of the cases to be discussed later (tartaric acid + sodium bicarbonate) this is true (in spite of the fact that the tablet can, for all practical purposes, be anhydrous at the onset).

The most common type of interaction in solid dosage forms is actually between water and drug. This is a large topic in itself, and Chap. 15 is devoted to it. The topic discussed here will be of special cases in which water is not the interactant (or the main interactant).

The following illustrative examples will be discussed:

1. Tartaric acid and sodium bicarbonate
2. Aspirin and phenylephrine
3. Aspirin and lubricants

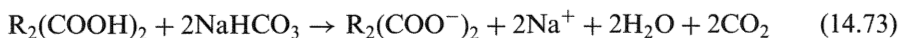
In addition to the points made, it is noted in the curve in Fig. 14.24 that a lag time sometimes has to be invoked for the data to linearize.

The formation of molecular compounds as discussed in Chap. 11, under the heading of *Eutectics*, is a type of solid-state interaction. It, at times, is of importance in solid dosage form formulation. For instance, the author was in charge of the scale-up of a soft-shell capsule product, Filibon, once marketed by American Cyanamid Company (Lederle). It contained among other vitamins, niacinamide and ascorbic acid. In small scale, in which time lapses are short, the product was quite “stable,” but in large-scale production, during which the capsule contents were exposed to the moisture in the soft shell for longer times, the capsule “hardened up,” in fact became a “bullet.” The product was a (molecular compound type) interaction between niacinamide and ascorbate, and the problem was rectified by carrying out the reaction before blending the powders. The niacinamide and ascorbic acid were simply mixed in a blender and “granulated” with ethanol. The resulting powder was bright yellow. When dissolved in water the individual components will regenerate.

There have been occasional reports of solid-state interactions in the pharmaceutical literature. Bogdanova et al. (1998) have shown a solid-state interaction between indomethacin and nicotinamide. The solubility of the complex varies in a fashion, such that the solubility is maximum at a given indomethacin concentration.

14.9.1. Tartaric Acid and Sodium Bicarbonate

This is a common combination in effervescent tablets. When the tablet is added to water, the acid and the base will react, forming carbon dioxide, which produces the desired bubble effect.



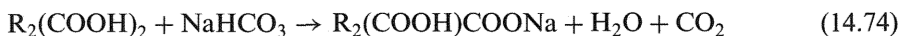
To be strictly correct, the left-hand side should be written in ionic form as well.

It is necessary that this reaction does not take place before the time it reaches the consumer, because if the reaction does occur in the solid state, then (a) carbon dioxide will form in the container, (b) the tablet will become softer, and (c) on “reconstitution” the bubble effect will be reduced to the extent carbon dioxide was lost in storage.

The evolution of carbon dioxide would normally build up pressure in a glass bottle, but the tubes in which effervescent products used to be sold were not tight, and the carbon dioxide could escape. The same is true to a great extent in plastic bottle and in plastic blister packs, but the problem that the reaction (as shall be demonstrated later) is catalyzed by moisture, in other words, that the container is not hermetic in this aspect, is a disadvantage. This is so sensitive that during manufacture extra precautions are taken to keep the relative humidity of the processing areas low. Hence, one must also pack the products in hermetic containers, and the aluminum foil has become a popular means of doing this. If, however, the initial moisture is not low enough, then the reaction will proceed, and the internal pressure will cause the aluminum foil to “balloon.”

The solid-state reaction has been investigated by Usui and Carstensen (1986) and Wright and Carstensen (1987). When the reaction occurs in the solid state, there are two questions that present themselves:

1. Is moisture important, and if so in what sense?
2. What is the stoichiometry? Is it that of Eq. (14.73) or is it



Usui checked the weight loss of heated samples in hermetic containers, utilizing different ratios of acid and base and established that the stoichiometry is that of Eq. (14.74); that is, the mole-to-mole interaction of tartaric acid and sodium bicarbonate.

He next studied the weight loss in open containers and demonstrated that the tartaric acid did not lose weight, and that the sodium bicarbonate and the mixture of sodium bicarbonate and tartaric acid, lost weight at a low rate, corresponding to that of the sodium bicarbonate itself. In other words in an open container, there was no interaction, simply decarboxylation of the bicarbonate itself.

He next studied the effect of compression on the decomposition of sodium bicarbonate. Characteristic curves are shown in Fig. 14.25. It is noted that the decomposition rates are a function of applied pressure. In the following it is assumed that the particles are isometric and that the reaction rate is proportional to the surface area of unreacted sodium bicarbonate. The following nomenclature is used: there are M g of unreacted sodium bicarbonate at time t , and M_0 initially. There are N particles each of area a , volume v and density ρ . The surface area is proportional to the two-thirds power of the volume by the isometry factor Γ , that is,

$$a = \Gamma v^{2/3} = \Gamma \rho^{2/3} m^{2/3} \quad (14.75)$$

$$A = N \Gamma \rho^{-2/3} m^{2/3} = N^{1/3} \Gamma \rho^{-2/3} M^{2/3} \quad (14.76)$$

It follows that

$$A_0 = N^{1/3} \Gamma \rho^{-2/3} M_0^{2/3} \quad (14.77)$$

The decomposition rate is proportional to the surface area at time t ; that is,

$$dM/dt = -k'' A = -k' M^{2/3} \quad (14.78)$$

where

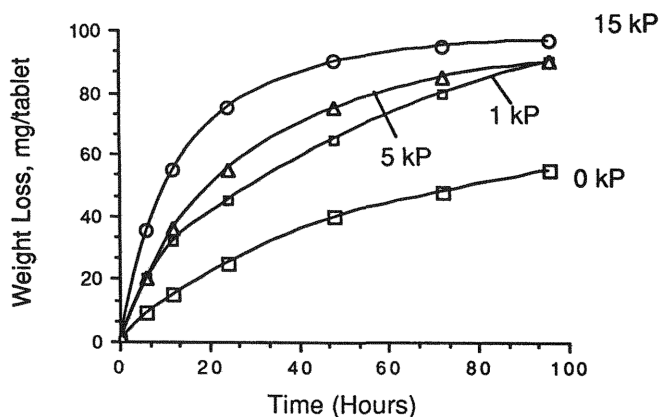


Fig. 14.25 Effect of tableting pressure on sodium bicarbonate decomposition at 70°C. (Data from Usui and Carstensen, 1985.)

$$k' = k'' N^{1/3} \Gamma \rho^{-2/3} \quad (14.79)$$

Rearrangement of Eq. (14.78) gives

$$dM/M^{2/3} = k' t \quad (14.80)$$

This may be integrated, and when initial conditions are imposed the following expression results:

$$(M/M_0)^{1/3} = (1 - x)^{1/3} = 1 - kt \quad (14.81)$$

where x is mole fraction decomposed, and where

$$k = k'' N^{1/3} \Gamma \rho^{-2/3} / [3M_0^{1/3}] \quad (14.82)$$

Eliminating N by inserting Eq. (14.77) into Eq. (14.82) gives

$$k = k'' A_0 / (3M_0) \quad (14.83)$$

The data should, therefore, plot by a cube-root equation and Fig. 14.26, indeed, shows this to be so.

The rate constants according to Eq. (14.83) should be proportional to the specific surface area at time zero (A_0/M_0). That this is true is shown in Fig. 14.27. The rate constants follow an Arrhenius plot, and are in line with the data reported by Schefter et al. (1974).

In a closed system there is a rapid interaction between the sodium bicarbonate and tartaric acid in compressed tablets. Even though the system is supposedly dry, it is assumed that there is a very slight amount (z mol) of water present in the tablet initially and that the reaction starts in a dissolved stage. If this is true, then, as water is produced in the reaction, there will be an acceleration. The data can be modeled in the fashion shown in the following. The nomenclature used is: M' is the number of moles of sodium bicarbonate left at time t , and M'_0 is the initial number of moles, S is its solubility in water and C is the concentration in the water present at time t . S_1 is the solubility of the tartaric acid in water.

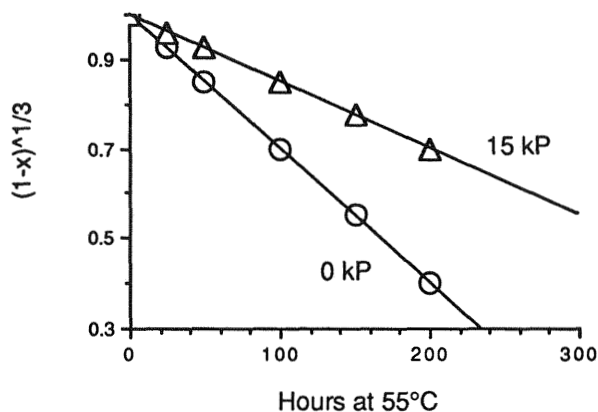


Fig. 14.26 Cube-root plot of sodium bicarbonate decomposition at 55°C: least-squares fit equations: 0 kP; $y = 1 - 0.0015x$ ($R = 100$), and 15 kP; $y = 1 - 0.003x$ ($R = 1.00$). (Data from Usui and Carstensen, 1985.)

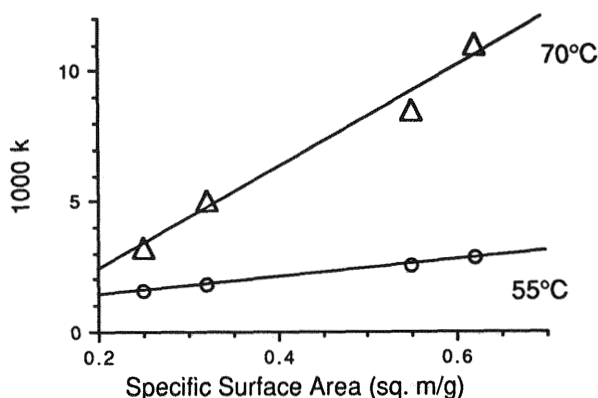


Fig. 14.27 Cube-root constants from Fig. 14.25 versus specific surface areas: least-squares fits; 70°C, $y = -1.534 + 19.447x$ ($R = 0.99$); and 55°C, $y = 0.788 + 3.188x$ ($R = 1.00$). (Data from Usui and Carstensen, 1985.)

According to the reaction scheme the number of moles of water present at time t then is

$$(M'_0 - M' + z)\text{mol} = (M'_0 - M' + z)0.018 \quad (14.84)$$

The disappearance rate of sodium bicarbonate in solution is given by

$$-dC/dt = k_2 S_1 S \quad (14.85)$$

where k_2 is the second-order rate constant. To express this as number of moles decomposed, this figure is multiplied by the volume of water present [i.e., the expression in Eq. (14.84)]:

$$dM'/dt = -k * (M'_0 - M' + z) \quad (14.86)$$

where

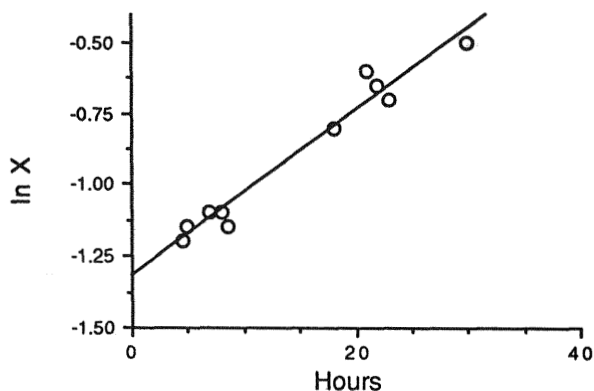


Fig. 14.28 Decomposition of tartaric acid plus sodium bicarbonate tablets at 55°C (5 kP force): least-squares fit; $\ln\{X\} = -1.3225 + 0.0291 \cdot t$ ($R = 0.98$). (Data from Usui and Carstensen, 1985.)

$$k^* = 0.018k_2S_1S \quad (14.87)$$

Equation (14.86) can now be recast in the following form:

$$\ln(M'_0 - M' + z) = k^*t + \ln[z] \quad (14.88)$$

or, employing x , the mole fraction decomposed is

$$\ln[x + (z/M_0)] = k^*t + \ln[z/M'_0] \quad (14.89)$$

Recalling that z is a small number, the term z/M_0 is small, and Eq. (14.89) then simplifies to

$$\ln[x] = k^*t + \ln(z/M'_0) \quad (14.90)$$

Data are plotted in this fashion in Fig. 14.28. It is seen that the linearity is quite good. The value of z may be estimated from the intercept and comes to about 0.1 mg/tablet, which is a reasonable figure. This, in essence, shows that the theories suggested by Wright (1983) are correct.

It is obviously of pharmaceutical importance in most situations to slow down the reaction in the solid state, and yet maintain the reactivity in the solid state. (An exception to this is when a reaction is purposely carried out during a granulation, for instance). One way of retarding the reaction rate is to preheat the bicarbonate to 95°C for a certain length of time (White, 1963; Mohrle, 1980). This will react by the scheme



The water formed granulates the mixture, and makes it easier to compress. But more importantly the sodium carbonate formed can form double salts with the bicarbonate. These are dodecahydrates, and act as moisture scavengers. They hence stabilize the acid/base mixture in the solid state (if reasonable moisture barriers are provided): any *small* amount of moisture created by a beginning reaction of the type of Eqs. (14.73) or (14.74), will react with a mixture of the carbonate and bicarbonate to form a double salt hydrate.

14.10. pH OF THE MICROENVIRONMENT

In the strictest sense, pH is not a term that is defined in a solid system. For it to have meaning, there must be some water mediation, but both tocopheryl acetate and calcium pantothenate are cases in point. The former is sensitive to high pH, the former to low pH. Calcium pantothenate is frequently admixed with magnesium oxide and granulated separately from the remaining ingredients. In this manner an alkaline microenvironment is created, which ascertains the stability of the vitamin.

In the case of tocopheryl acetate, the hydrolysis is accelerated by hydroxyl ions. Again it is noted that the reaction must be associated with some dissolution step in small amounts of water. The produced tocopherol is much less stable; hence, the hydrolysis and the presence of water are contraindicated. This is a particular instance where the use of alkaline excipients (e.g., hydroxyapatite) can be deleterious at higher temperatures. In the absence of (or at low levels of) moisture the reaction may not proceed. It is also characteristic that often, higher temperatures are not indicative of what will happen at room temperature.

If it is desired to control the pH of the microenvironment then citric, tartaric, and fumaric acids are the acids of choice. They are, however, all corrosive, and their pharmaceutical handling is far from ideal. With an alkali, sodium bicarbonate, sodium carbonate, and magnesium and calcium oxides are common, and are not as corrosive as the acids mentioned, but they are abrasive, and they, too, are not the most ideal substances to handle in a tablet or capsule.

For certain compounds it is necessary to control the "microenvironment" in even more drastic fashion. Gu et al. (1990) report on drug excipient incompatibility studies of moexipril hydrochloride, and demonstrate that (even "wet") adjustment of the microenvironmental pH (i.e., adding small amounts of water to a mixture of the drug with sodium bicarbonate or sodium carbonate), did not sufficiently stabilize the mix. But when the mixture was *wet granulated*, and when *stoichiometric amounts of alkali were used*, then stabilization resulted. This essentially means that, in the solid state, *the sodium salt is stable* as opposed to the acid. It might be argued that in such a situation the sodium salt should be manufactured and used as such. It might be argued that it should be claimed as the active ingredient (equivalent to a certain amount of free acid, or in amphoteric substances, the acid addition salt), but often the salt is very soluble and hygroscopic (e.g., potassium clavulanate); hence, they are difficult to produce. The situation is referred to in the *Federal Register* as a *derivative drug*.

14.11. PSEUDOPOLYMORPHIC TRANSFORMATIONS

Dehydration, as mentioned before, may result in amorphous anhydrides, but may also result in another crystalline phase (e.g., a lower hydrate or a crystalline anhydrate). These are, properly speaking, *pseudopolymorphic transformations*. There are several steps in dehydration of a hydrate, and they may be summarized in the following manner, where S denotes solid, D denotes drug, V denotes vapor, and L denotes liquid (Han and Suryanarayanan, 1997).



that is,

$$\Delta H_T = \Delta H_v + \Delta H_s \quad (14.92)$$

so that different results may be obtained in DSC experiments depending on whether a crimped or open pan is used.

Bray et al. (1999) have shown such a diagram for [2(S)-[*p*-toluenesulfonyl amino]-3-[[[5,6,7,8-tetrahydro-4-oxo-5-{5-[2-(piperidin-4-yl)ethyl]-4-*H*-pyrazolo[1,5-*a*][1,4]diazepin-2-yl]carbonyl]amino]-propionic acid.

Suihko et al., (1997) have employed DSC to show that dehydration of theophylline monohydrate is a two-step process.

14.12. EQUILIBRIA AND EFFECTS OF APPLIED PRESSURE

There are times in which equilibrium sets up in the solid state. Vitamin A beadlets equilibrate at about 75% of the original vitamin A potency, and tocopherol acetate, likewise, can achieve an equilibrium state in solid-dosage forms. These equilibria may, or may not, be pressure induced.

More convincingly, Wurster and Ternik (1995) have reported data that imply a pressure-induced activity loss in solid-state catalase (Figs. 14.29 and 14.30). There may not be a total loss, even at high pressures, because the figures seem to taper off with increasing pressure, and by iteration it may be found that, expressing the numbers as percent, 67% of activity left, even at high pressure, gives the best bias fit, and this is shown in Fig. 14.30.

14.13. PHOTOLYSIS IN THE SOLID STATE

Not much systematic work has been reported on photolysis of solids. Lachman et al. (1961) pointed out that, most often, a solid tablet will decompose by photolytic decomposition only in the surface area, so that if one broke a “discolored,” exposed tablet, then the color would be unaffected in the interior.

However, Kaminski et al. (1979) reported on a case where a combination of moisture and light caused an interaction between a dye and a drug (ethinyl estradiol) that permeated the entire tablet. Tønnesen et al. (1997) have reported on the photo-reactivity of mefloquine hydrochloride in the solid state.

14.14. CHOICE OF MODEL

Carstensen (1980) noted that topical reaction profiles were literally indistinguishable from first-order decomposition profiles. It *is* possible, at times, to invoke Arrhenius fitting to distinguish between reaction mechanisms as pointed out by Nelson et al. (1974), and at times, valuable information may be gleaned in this fashion. However, (Carstensen, 1977) Arrhenius plotting of a first-order reaction, and the same data treated by zero-order kinetics give fairly much the same goodness of fit and activation energy.

Often, data are fitted to a series of equations, and the model chosen is the one that fits the data “the best” (Sharp et al., 1996). Carstensen (1995), Sharp et al.

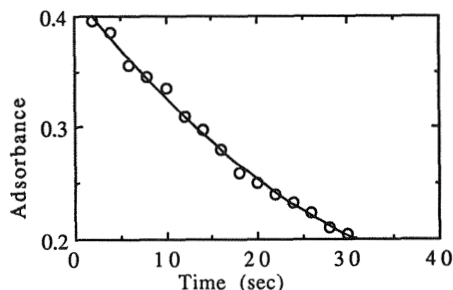


Fig. 14.29 Activity loss of catalase in the solid state induced by pressure. (Data from Wurster and Ternik, 1995.)

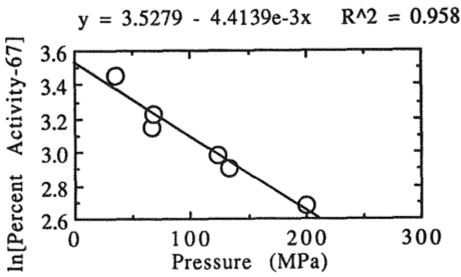


Fig. 14.30 Data from Fig. 14.29 treated by subtracting 67% from the percentage of zero pressure content, and plotting loglinearly against applied pressure. Figure is not part of the reference publication. (Data from Wurster and Ternic, 1995.)

(1996), Ledwige and Corrigan (1996), and Taylor and York (1998) have cautioned against that “lack of discrimination of the different best fitting models.”

The original suggestions by Nelson et al. (1974) and Carstensen (1980) were investigated by Taylor and York (1998), who fitted dehydration data to a series of oft-used kinetic equation and applied the rate constants to the Arrhenius equation. They, as did Carstensen (1980), found that fits and activation energies from the different models remained fairly invariant.

At times, models can be *ruled out*. The data in Fig. 14.31 is the data in Table 14.6 treated by the Prout–Tompkins equation. It is seen that there is definite curvature in the plot, sufficient to rule out the model as representing the decomposition mechanism.

14.15. INTERACTIONS INVOLVING A LIQUID PHASE

At times an active ingredient or a decomposition product in a solid dosage form is a liquid, and this may interact with other ingredients in the dosage form. A typical example is the work by Troup and Mitchner (1964) dealing with aspirin and phenylephrine. The authors showed that the decomposition of phenylephrine was linearly related to the formation of salicylic acid. They showed that the decomposition of phenylephrine was an acetylation. This can be thought of in many ways. There has to be some moisture present to permit the hydrolysis of aspirin. If the salicylic acid is

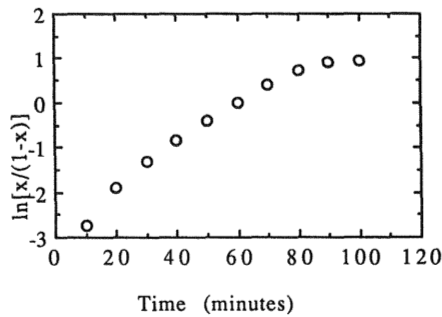
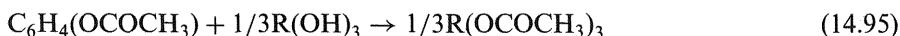
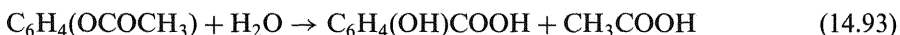


Fig. 14.31 Data from Table 14.4 treated by Prout–Tompkins kinetics.

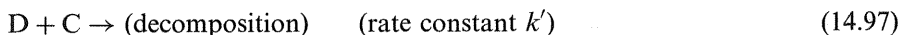
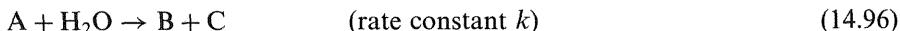
formed by interaction of aspirin with traces of water, then the acetic acid formed may react with the phenylephrine $[R(OH)_3]$, again liberating water, so that the moisture does not play a part, quantitatively in the overall reaction, in other words



An alternate explanation would be that phenylephrine interacted directly with aspirin in an anhydrous solid state to transacetylate, which is not probable. The question is whether the acetic acid (which has a sizable vapor pressure) interacts with the phenylephrine as a gas with a solid reaction (to be covered shortly) or as a liquid with a solid reaction.

There are other examples of the interaction of acetic acid with active ingredients (e.g., the work by Jacobs et al., 1966, in which acetylation of codeine in aspirin/codeine combinations was demonstrated). Again, whether the acetylation is achieved by acetic acid in the vapor phase or in the liquid state or (more unlikely) whether it is a direct solid-to-solid interaction, is not yet resolved. If it were the latter, then Jander kinetics should actually apply. But it is difficult to distinguish this and pseudo-first-order reactions. If it is an interaction in the liquid state, then it probably occurs by the phenylephrine dissolving in the acetic acid formed.

In more general terms, it is assumed that there are two drugs, A and D. A decomposes (e.g., by hydrolysis) to form a liquid decomposition product C. The reactions then are:



C is the species that is liquid. In this case a saturated solution (S mol/mol) of D in C is formed, and it is assumed that dissolution is fast. Let A be the number of moles of drug present at time t , C the number of moles of acetic acid, and let M denote the molarity of the liquid decomposition product (e.g., for acetic acid at 25°C the density is 1.05 g/mL, so that, because its molecular weight is 60, M would be $1005/60 = 16.75$). The rate at which D disappears is the question to be solved. It is assumed that the disappearance rate of A is pseudo-first-order, that is

$$A = A_0 \exp(-kt) \quad (14.98)$$

The disappearance rate of D depends on how much C is present, so the equation for C must first be established and solved. C is created at a rate of kA , but it is consumed by D. The rate of the latter step is given by a second-order reaction term. The concentration of D is S , and the molecular weight of C is M . The amount of C at time t is C , so that (in terms of moles)

$$dC/dt = kA - k'SCM \quad (14.99)$$

Inserting Eq. (14.98), using and denoting

$$k'SM = a \quad (14.100)$$

where a is constant, we arrive at the following equation:

$$dC/dt = kA_0 \exp(-kt) - aC \quad (14.101)$$

Laplace transformation, using L-notation, gives:

$$sL - 0 = [kA_0/(s+k)]aL \quad (14.102)$$

or

$$L = [kA_0/(a-k)][\{1/(s+k)\} - \{1/(s+a)\}] \quad (14.103)$$

so by taking anti-Laplacians

$$C = [kA_0/(k'SM - k)]\{\exp(-kt) - \exp(-k'SMt)\} \quad (14.104)$$

It follows that the decomposition rate of D is given by

$$dD/dt = k'SCM = aC \quad (14.105)$$

by integrating Eq. (14.105) and multiplying by a , we obtain

$$D = [kaA_0/(k'SM - k)]\{[\{\exp(-k'SMt)\}/k'SM] - (\{\exp(-kt)\}/k)\} \quad (14.106)$$

An example of this is shown in Fig. 14.32 using $A = 50$, $k = 0.2$, and $k'SM = 0.1$. A different situation arises when an insoluble component interacts with a drug in solution (or vice versa). An example of this is the interaction between microcrystalline cellulose ($R'CHOHR''$) and substituted furoic acids ($RCOOH$) (Carstensen and Kothari, 1983). The furoic acids decompose when heated by themselves, into a liquid decomposition product and carbon dioxide. In the presence of microcrystalline cellulose, however, the mixture forms carbon monoxide:



Q is a liquid, which will dissolve furoic acid to the extent of its solubility, and will spread over the microcrystalline cellulose. There will be a number of contact points N , at which interaction can take place (essentially the "wetted" part of the microcrystalline cellulose). There will be a reaction probability a , associated with each contact point. The reaction accelerates because the larger the extent it has reacted, the more liquid there will be to dissolve the furoic acid; hence, the more contact points. At a

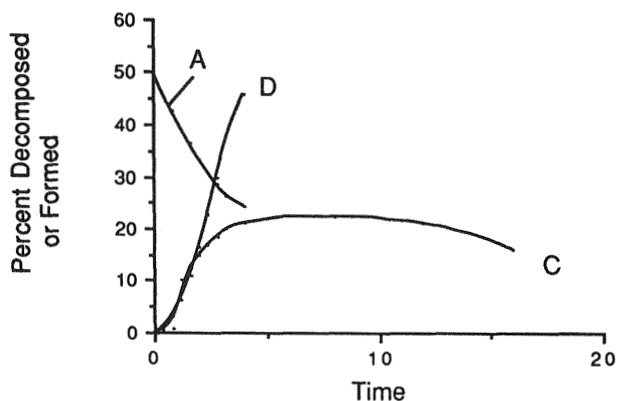


Fig. 14.32 Stability profile using $A = 50$, $k = 0.2$, and $a = 1$.

given time point there will be overcrowding, because dissolved molecules will be next to contact points that have already reacted. Hence, there is also a termination probability b . But unlike the Prout-Tompkins model, this is finite at time zero.

It might be argued that the external surface of the microcrystalline cellulose would be insufficient to account for the total decomposition. There are, however, two types of surface present in microcrystalline cellulose: nitrogen adsorption gives low surface areas (the external area); whereas, for instance, water isotherms give surface areas 100 times as large (Hollenbeck, 1978; Marshall et al., 1972; Zografis and Kontny, 1986).

By the decomposition at a contact point, it is assumed that the decomposition, creating one liquid decomposition molecule, will dislodge (dissolve) S molecules of furoic acid at the contact point. If the initial number of contact points is N_0 , then

$$dN/dt = [-b + a(S - 1)]N = qN \quad (14.108)$$

where $q = -b + a(S - 1)$. The factor arises from the fact that when a molecules react, then aS new contact points are created and one (the one at which the reaction took place) is lost.

It follows then from integrating Eq. (14.108) (which can be done, since a and b are assumed constant), that

$$N = N_0 \exp(qt) \quad (14.109)$$

Since, at a given time t , the rate of decomposition is proportional to the number of contact points, then, L being the number of intact alkoxyfuroic acid molecules

$$dL/dt = gN \quad (14.110)$$

where g is a constant. From the definition of L it follows that the mole fraction x decomposed is given by

$$x = (L_0 - L)/L_0 \quad (14.111)$$

or

$$dx/dt = -(1/L_0)dL/dt \quad (14.112)$$

Equation (14.110) inserted in this gives

$$dx/dt = (1/L_0)gN \quad (14.113)$$

Substituting Eq. (14.109) into this gives

$$dx/dt = (gN_0/L_0) \exp(qt) \quad (14.114)$$

This integrates to

$$x = (gN_0/(L_0q))[e^{qt} - 1] = [e^{qt} - 1]/A \quad (14.115)$$

where the term $A = (L_0q/gN_0)$ has been introduced for convenience. Equation (14.115) is equivalent to

$$\ln[1 + Ax] = qt \quad (14.116)$$

Figure 14.33 shows data treated in this fashion.

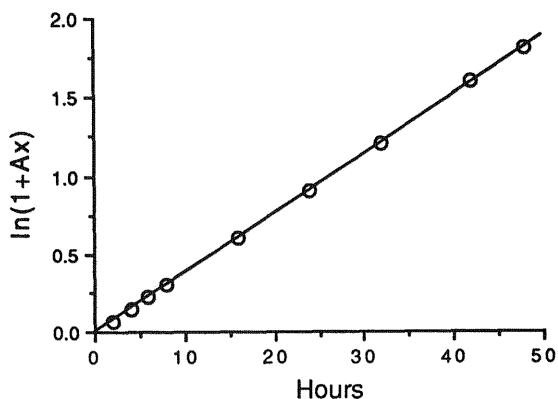


Fig. 14.33 Furoic acid data treated according to Eq. (14.116). (Data from Carstensen and Kothari, 1983.)

14.16. CASES OF INTERACTION OF A LIQUID WITH A POORLY SOLUBLE DRUG

There are cases for which there are liquids in a solid dosage form. An example is panthenol in a multivitamin tablet. Here it is customary to adsorb the liquid onto a solid carrier and for panthenol, magnesium trisilicate is used. At elevated temperatures (and at room temperature under compression as well) the panthenol will ooze out of the carrier, and come in intimate contact with other solids. If interaction potentials exist, then separation techniques, such as triple-layer tablets (or compression-coated tablets) are resorted to. Here, the liquid will still ooze into the layer containing its interactant, but the process will be diffusion controlled. It can be shown (Jost, 1962) that the average concentration C of the liquid in the neighboring layer with which it is in contact, is given by:

$$(C - C_f)/(C_0 - C_f) = Qe^{-kt} \quad (14.117)$$

where C_f is the concentration at infinite time. The term on the right-hand side is actually the leading term of an infinite series.

14.17. REACTIONS VIA THE GAS PHASE

Sometimes the vapor pressure of a drug is sufficiently high that it may interact with other substances via the vapor phase. An example is ibuprofen (B). This is a Lewis acid, and may interact with Lewis bases. Usual measures, such as triple-layer tablets, do not work in this case, for the interactant will be present in the gas phase.

If the reaction with another drug (D) is



then the initial reaction rate is given by

$$d\{D\}/dt = kP_B[D]A \quad (14.119)$$

where $\{D\}$ is the surface density of D -molecules (number of molecules/cm²) at time t and A is the surface area. As long as there is no penetration into the crystals, the reaction will, therefore, be a first-order reaction, since Eq. (14.119) integrates to

$$\ln[D] = -kAP_B t + \ln[D_0] \quad (14.120)$$

where D_0 is the initial concentration. This will be true if only the surface of the solid interactant is affected. The extent of decomposition will be slight, because (unless the drug is extremely finely subdivided) only a small fraction of the molecules are on the surface. If, however, the ibuprofen penetrates the crystal, then Jander kinetics should prevail. A similar situation may be at work in the aspirin incompatibilities mentioned earlier.

SYMBOLS

- A = number of moles of unreacted solid at time t
- A_0 = original number of moles of unreacted solid
- a = side of a cube at a time t after reaction has started
- a_0 = side of a cube before decomposition
- $B = (k_1/k_s) - 1 - S$ = iterant in the Bawn equation
- C = (a) general symbol for concentration, (b) concentration in the water present in an effervescent tablet at time t
- C_1 = constant in the WLF equation
- C_2 = constant in the WLF equation
- C_f = the concentration at infinite time
- D = diffusion coefficient
- DSC = differential scanning calorimetry
- E = energy
- E_a = activation energy
- $E_{>_i}$ = energy levels above E_i
- F = (a) a constant, (b) preexponential constant in first-order decay
- H = height of a cylinder
- ΔH = heat of fusion
- ΔH_d = enthalpy of dehydration
- ΔH_f = enthalpy of transition
- ΔH_v = enthalpy of vaporization
- h = thickness of a reacted layer
- k = general term for rate constant
- k_1 = first-order rate constant
- k_2 = rate constant for two-dimensional diffusional decomposition
- k^* = rate constant in effervescent interaction
- L = (a) symbol for Laplace operator, (b) number of intact alkoxyfuroic acid molecules at time t
- L_0 = number of intact alkoxyfuroic acid molecules, initially
- M = mass of intact sample at time t
- M_0 = initial mass of intact sample
- M' = number of moles of sodium bicarbonate left at time t
- M'_0 = initial number of moles of sodium bicarbonate
- m = mass not reacted

- N = (a) number of nuclei, (b) number of particles in a sample
 N_0 = initial number of intact molecules
 N_1, N_2, N_3 = number of nuclei in one, two or three dimensions in approximate Avrami model
 $N_{>E_i}$ = number of molecules with energy levels above E_i
 n = (a) exponent in the Ng equation, (b) an integer between 1 and 4 (Avrami–Erofeyef equation)
 p = exponent in the Ng equation
 Q = constant in the expanded Avrami model
 Q_1 = (a) constant in the slow-nucleation, fast-reaction model, (b) $[qk^n/(n+1)]$, a constant in the Avrami treatment
 q = constant in the (a) Avrami treatment, (b) the Arrhenius equation, (c) Jander equation
 R = (a) ideal gas constant, (b) property (e.g., heat capacity or rate constant) of an amorphate at a temperature below or above its glass transition temperature, (c) radius of a cylinder
 R_g = the property R of an amorphate at the glass transition temperature
 S = (a) solubility in water (for components of effervescent tablet), (b) S = solubility (mol/mol) of a solid compound in its liquid decomposition product
 S_1 = solubility of tartaric acid in water
 T = absolute temperature, K
 T^* = eutectic temperature
 T_f = melting point
 T_g = glass transition temperature
 $T_{\max}$ = temperature at the peak maximum in a DSC
 t = time
 t_l = lag time
 v = particle volume
WLF = Williams–Landel–Ferry
 x = (a) fraction, (b) mole fraction, (c) fraction decomposed, (d) number of moles of water in a hydrate
 x^* = the mole fraction in Bawn kinetics where just enough material has decomposed to just dissolve the remainder of the parent compound
 Z = normal standard deviate
 z = original, very small amount of water present in an effervescent tablet
 α = propagation probability or rate
 β = termination probability or rate
 Γ = shape factor
 ϕ = the rate of heating
 ρ = density of a solid

REFERENCES

- Adler M, Lee G (1999). *J Pharm Sci* 88:199.
Agbada CO, York P (1994). *Int J Pharm* 106:33.
Anderson NR, Banker GS, Peck GE (1982). *J Pharm Sci* 71:7.
Avrami M (1939). *J Chem Phys* 7:1103.

- Avrami M (1940). *J Chem Phys* 8:212.
- Avrami M (1941). *J Chem Phys* 9:177.
- Bogdanova S, Sidzhakova D, Karaivanova V, Georgieva S (1998). *Int J Pharm* 163:1.
- Bray ML, Jahansou H, Kaufman MJ (1999). *Pharm Dev Technol* 4:81.
- Byrn SR (1982). *Solid State Chemistry of Drugs*. Academic Press, New York, pp 59–70.
- Carstensen JT (1980) *Solid Pharmaceutics: Mechanical Properties and Rate Phenomena*. Academic Press, New York.
- Carstensen JT, Kothari R (1983). *J Pharm Sci* 72:1149.
- Carstensen JT, Van Scoik K (1990). *Pharm Res* 7:1278.
- Carstensen JT, Morris T (1993). *J Pharm Sci* 82:657.
- Carstensen JT, Musa MN (1972). *J Pharm Sci* 61:273, 1112.
- Carstensen JT, Pothisiri P (1975). *J Pharm Sci* 64:37.
- Carstensen JT, Aron E, Spera D, Vance JJ (1966). *J Pharm Sci* 55:561.
- Carstensen JT, Franchini M, Pudipeddi M, Morris T (1993). *Drug Dev Ind Pharm* 19:1811.
- Dali MV (1995). Personal Communication
- Dudu SP, Das NG, Kelly TP, Sokoloski TD (1995). *Int J Pharm* 114:247.
- Erofeyev CR (1946). *CR Acad Sci URSS* 52:511.
- Finì A, Fazio G, Alvarez-Fuentes J, Fernández-Hervàs, Holgado MA (1999). *Int J Pharm* 181:11.
- Franks F. (1989). *Process Biochem* 24:3–8.
- Gu L, Strickley RG, Chi L-HH, Chowhan ZT. (1990). *Pharm Res*. 7:379.
- Han J, Suryanarayanan R (1997). *Int J Pharm* 157:209.
- Hollenbeck RG, Peck GE, Kildsig DO (1978). *J Pharm Sci* 67:1599.
- Imaizini H, Nambu N, Nagai T (1980). *Chem Pharm Bull* 28:2565.
- Gubskaya AV, Lisnyak YV, Blagoy YP (1995). *Drug Dev Ind Pharm* 21:1953.
- Jacobs A, Dilatusch A, Weinstein S, Windheuser J (1966). *J Pharm Sci* 53:893.
- Jander W (1927). *Z Anorg Chem* 163:1.
- Johnson WA, Mehl RF (1939). *Trans Am Inst Min Eng* 135:416.
- Jost H (1962). *Diffusion*. Academic Press, New York, p 45.
- Kaminski EE, Cohn RM, McGuire JL, Carstensen JT (1979). *J Pharm Sci* 68:368.
- Kissinger HE (1956). *J Res Nat Bur Stand* 57:217.
- Kittel C (1956). *Introduction to Solid State Physics*, 2nd ed. John Wiley & Sons, New York.
- Lachman L, Weinstein S, Swartz C, Urbanyi T, Cooper J (1961). *J Pharm Sci* 50:141.
- Lemmon RM, Gordon PK, Parsons MA, Mazetti F (1958). *J Am Chem Soc* 80:2730.
- Lennard-Jones JE (1931). *Proc Phys Soc (Lond)* 43:461.
- Leung SS, Padden BE, Munson EJ, Grant DJW (1998a). *J Pharm Sci* 87:501.
- Leung SS, Padden BE, Munson EJ, Grant DJW (1998b). *J Pharm Sci* 87:509.
- Lin CT, Birn SR (1979). *Mol Cryst Liq Cryst* 50:99.
- Lo PKA (1977). A study of the solid state stability of ampicillin. PhD dissertation, University of New York at Buffalo.
- Marshall K, Sixsmith D, Stanley-Wood NG (1972). *J Pharm Pharmacol* 24:138.
- Moelwyn-Hughes EA (1961). *Physical Chemistry*, 2nd revised ed. Pergamon Press, New York, p 31.
- Mohrle R (1980). In: Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms: Tablets*, vol 1. Marcel Dekker, New York, p 24.
- Nelson E, Eppich D, Carstensen JT (1974). *J Pharm Sci* 63:755.
- Ng WL (1975). *Aust J Chem* 28:1169.
- Oberholtzer ER, Brenner GS (1979). *J Pharm Sci* 68:863.
- O'Donnel JH, Whittaker AK (1992). *JMS Pure Appl Chem* A29:1–10.
- Oksanen CA, Zografi G (1993). *Pharm Res* 10:791.
- Olsen BA, Perry FM, Snorek SV, Lewellen PL (1997). *Pharm Dev Technol* 2:303.
- Otsuka M, Ofusa T, Yoshihisa M (1999). *Drug Dev Ind Pharm* 25:197.

- Otsuka M, Onoe M, Matsuda Y (1993). *Pharm Res* 10:577.
- Otsuka M, Teraoka R, Matsuda Y (1991). *Pharm Res* 8:1066.
- Pfeiffer RR, Engel GL, Coleman D (1976). *Antimicrob Agents Chemother* 9:848.
- Pikal MJ, Lukes AL, Lang JE, Gaines K (1976). *J Pharm Sci* 67:767.
- Pikal MJ, Lukes AL, Jang JE (1977). *J Pharm Sci* 66:1312.
- Pothisiri P, Carstensen JT (1976). *J Pharm Sci* 64:1931.
- Pudipeddi M (1995). Personal communication.
- Roy ML, Pikal MJ, Rickard EC, Maloney AM (1990). International Symposium on Product Biological Freeze-Drying and Formulation, Bethesda, MD. *Dev Biol Stand* 74:323–340. (Karger, Basel, 1991).
- Schmitt EA, Law D, Zhang GGZ (1991). *J Pharm Sci* 88:291.
- Shalaev EY, Shalaeva M, Burn SR, Zografi G (1997). *Int J Pharm* 152:75.
- Shefter E, Kmack G (1967). *J Pharm Sci* 56:1028.
- Shefter E, Lo A, Ramalingam S (1974). *Drug Dev Commun* 1(1):29.
- Shlyankevich A (1995). Personal communication.
- Stacey FW, Saucer JC, McKusick BC (1959). *J Am Chem Soc* 81:987.
- Suihko E, Ketolainen J, Poso A, Ahlgren M, Gynther J, Paronen P (1997). *Int J Pharm* 158:47.
- Sukenik CN, Bonopace JA, Mandel NS, Bergman RC, Lau P-Y, Wood G (1975). *J Am Chem Soc* 97:5290.
- Suzuki E, Shimomura K, Sekiguchiki I (1987). *Chem Pharm Bull* 37:493.
- Tønnesen HH, Skrede G, Martinsen BK (1997). *Drug Stability* 1:249.
- Troup A, Mitchner H (1964). *J Pharm Sci* 53:375.
- Tzannis ST, Prestrelski SJ (1999). *J Pharm Sci* 88:351.
- Usui F (1984). Master's dissertation, University of Wisconsin, School of Pharmacy, Madison, WI.
- Usui F, Carstensen JT (1985). *J Pharm Sci* 74:1293.
- Van Scoik K, Carstensen JT (1990). *Int J Pharm.* 58:185.
- White B (1963). US patent 3,105,1792.
- Williams ML, Landel RF, Ferry JD (1955). *J Am Chem Soc* 77:3701.
- Wright JL, Carstensen JT (1986). *J Pharm Sci.* 75:546.
- Wurster DE, Ternik RL (1995). *J Pharm Sci* 84:190–193.
- Zografi G, Kontny M (1986). *Pharm Res* 3:187.

This Page Intentionally Left Blank

15

Effect of Moisture on Solid-State Stability

15.1. Amorphates	268
15.2. Nonhydrate-Forming Drug Substances	268
15.3. Very Low Moisture Levels	268
15.4. Intermediate Moisture Levels	269
15.5. Moisture Amounts at the Critical Moisture Content	271
15.6. Bound Water	273
15.7. Excess Water	274
15.8. Microenvironmental pH	275
15.9. Hydrate-Forming Drugs	276
15.10. Presence of Buffers	277
Symbols	278
References	278

Stability of drug substances in dosage forms is affected not only by their chemistry, but also by their environment. Compatibility studies are generally carried out with new drug substances in combination with common tablet or capsule ingredients to ascertain that the excipients chosen are not detrimental to the integrity of the drug (or of as little damage as possible). When such programs are carried out, it is conventional (Carstensen et al., 1964) to study combinations both in the absence *and the presence of water*. This is because, of all the types of substances one encounters in tablet and capsule formulations, *in general, the most detrimental is water*.

The chapter to follow will deal with the nature of the interaction between water or water vapor with drug substances.

15.1. AMORPHATES

Amorphous substances in the presence of water degrade according to first-order kinetics (Pikal, 1977; Morris, 1990). This is not surprising in light of the previous findings that amorphates are somewhat like liquids. Carstensen and Van Scoik (1990) showed that water vapor pressure over amorphous sucrose that contained water corresponded to a value that could be extrapolated from the vapor pressure curve of unsaturated solutions of sucrose at the other end of the concentration spectrum. Hence, such systems may be considered solutions and, as such, should behave, kinetically, as solution systems.

15.2. NONHYDRATE-FORMING DRUG SUBSTANCES

If a substance does not form a hydrate, then moisture present on or in it will be of the types shown in Fig. 15.1. It can be moisture that is adsorbed in an amount less than that corresponding to a monolayer (see Fig. 15.1a), or starting to form a bilayer (see Fig. 15.1b), or a multilayer (not shown). Once the critical vapor pressure for the compound (the water vapor pressure over a saturated solution) is reached (see Fig. 15.1c), moisture will condense on the solid in form of a bulk, and this bulk moisture layer will dissolve drug substance to the extent that a saturated solution is formed. If the vapor pressure is larger than the critical vapor pressure, then water will adsorb until *all* the solid is dissolved and an unsaturated solution, corresponding in concentration to the vapor pressure in question, is formed (see Fig. 15.1d). More will be said about the situations in the following and, in particular, the situation leading to Fig. 15.1c will be discussed.

15.3. VERY LOW MOISTURE LEVELS

This situation is the one referred to in Fig. 15.1a. What would be expected here is that the surface moisture would interact with active sites, and that the reaction would proceed from these active sites. In this event (a) either the moisture acts solely in a catalytic sense (i.e., the decomposition is nonhydrolytic, or (b) the disappearance

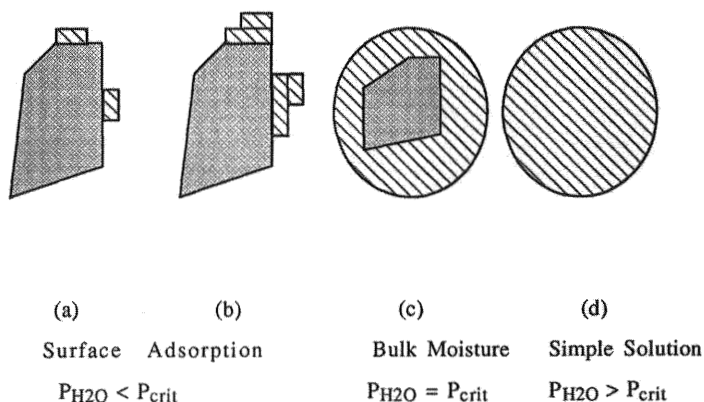


Fig. 15.1 Various stages of moisture adsorption on a crystalline solid.

of moisture is replenished (however small the coverage) in an amount determined by the isotherm. In either event, the decomposition will proceed along strings or planes, and this is akin to the Prout-Tompkins model described in Chap. 14. Figure 15.2 shows the situations described in Fig. 15.1 as it applies to *d*, *l*-leucovorin. At low water vapor pressure (square symbols), Prout-Tompkins kinetics apply, at very high moisture contents the situation in Fig. 15.1d applies, and the decomposition is simply solution kinetics (i.e., is first-order). Intermediate moisture levels, as shall be seen shortly, give rise to first-order kinetics.

The sigmoid profiles shown in Fig. 15.2 adhere well to the Prout-Tompkins equation

$$\ln[x/(1-x)] = k(t - t_{1/2}) \quad (15.1)$$

where x is fraction of drug activity retained, k is a rate constant (propagation constant), t is time and $t_{1/2}$ is half-life.

The development of such a model has been published by Attarchi (1984) and Carstensen and Attarchi (1988). Data plotted in this fashion is shown in Fig. 15.3, and the rate constants follow an Arrhenius equation (Fig. 15.4).

Literature data are most often insufficient to determine if BET sigmoidness accounts for the profile.. Leeson and Mattocks (1958), however, tied in aspirin decomposition in this region to a Freundlich-type isotherm.

15.4. INTERMEDIATE MOISTURE LEVELS

This is the part of Fig. 15.2 represented by triangles. This (as well as kinetics at very low moisture contents) have been explained in recent years by so-called hypotheses proposing amorphous-like "hot spots" on the surface of a solid. This is simply an extension of the concept of active sites when the subject is adsorption.

The hot spot theory is not new. In fact Gluzman (1954, 1956, 1958) and Gluzman and Arlozorov (1957) postulated that "part of a surface of a solid was actually in a liquid like state"—in other words, in appearance being a solid, but with random molecular arrangement, and usually referred to as an amorphate.

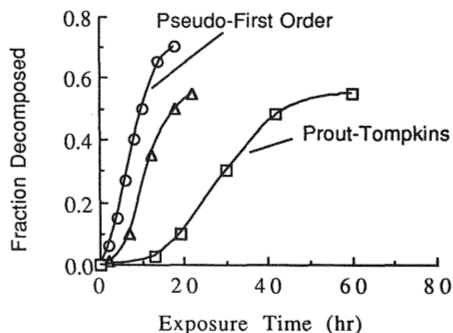


Fig. 15.2 *d*, *l*-Calcium leucovorin with moisture and buffers added. circles, 5% water with a pH 2.2 buffer in the solid state. (The buffer forms hydrates, and the water contents and percentages added are not necessarily available moisture); triangles, intermediate moisture content; squares, low moisture content.

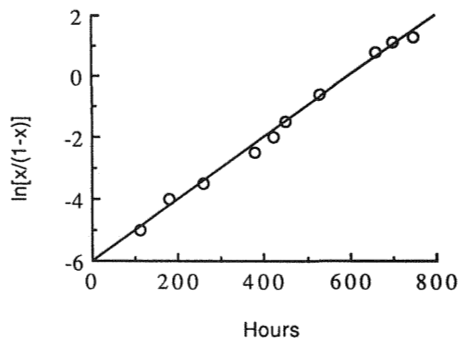


Fig. 15.3 Plot of aspirin decomposition data in the presence of low amounts of moisture. (Data from Carstensen and Attarchi, 1988.)

Guillory and Higuchi (1962) hypothesized that if such a theory were correct, then the logarithm of the rate constant at a given temperature T_d , of a series of analogous compounds in solid form should be inversely proportional to the inverse of the melting point, that is,

$$\ln[k] = -Q\{(1/T_d) - (1/T_m)\} \quad (15.2)$$

This has been true in certain cases (e.g., for vitamin A esters at 55°C) (Guillory and Higuchi, 1962), and substituted *p*-aminobenzoic acids (Carstensen and Musa, 1972), but in other cases (e.g., *p*-aminosalicylic acids), it does not hold well (Pothisiri and Carstensen, 1975).

The intermediate pattern (see triangles in Fig. 15.2) is often first order, and an explanation for this is forwarded in the following.

Figure 15.5 shows the situation during which a water molecule reacts with an activated drug molecule A^* . After reaction, the surface is lacking in one water molecule, which is then replenished from the atmosphere (Fig. 15.5). In this view the surface concentration of water molecules (however small) will remain constant (as long as the vapor phase does not significantly change).

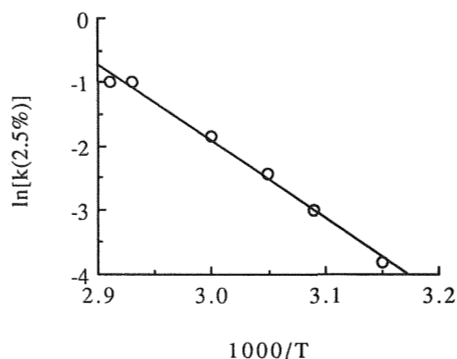


Fig. 15.4 Arrhenius plot of aspirin decomposition data in the presence of limited amounts of moisture. (Data from Carstensen and Attarchi, 1988.)

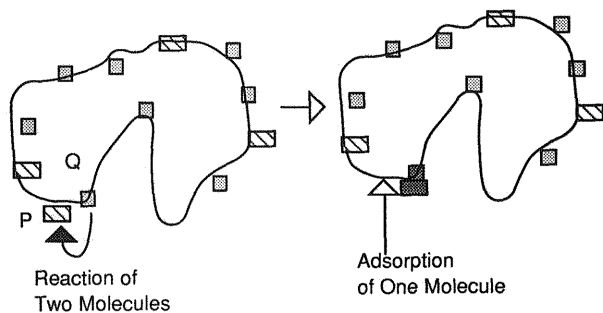


Fig. 15.5 Dotted squares represent activated A molecules, A^* , and dotted squares adsorbed moisture. In the first inset, an A^* molecule reacts with a water molecule and, in line with the isotherm a new water molecule is adsorbed (second inset).

Hence the disappearance rate of A^* is given by:

$$\partial\{A^*\}/\partial t = -k\{A^*\}[H_2O] = -k'\{A^*\} \quad (15.3)$$

since $[H_2O]$ is constant, where

$$k' = k[H_2O] \quad (15.4)$$

Equation (15.3) is a pseudo-first-order equation, explaining the intermediate kinetic behavior at intermediate moisture levels.

15.5. MOISTURE AMOUNTS AT THE CRITICAL MOISTURE CONTENT

It might, on the surface, seem unlikely that a drug substance in a closed system would experience exactly the critical vapor pressure, P_{crit} (i.e., the vapor pressure that equals that of a saturated solution).

However, many real-life examples give rise to exactly this situation. As shown in Fig. 15.6, an anhydrous sample of solid may be transferred to a bottle where the atmospheric water vapor pressure is above the critical water vapor pressure. The bottle is capped, and the system will equilibrate, moisture will condense onto the

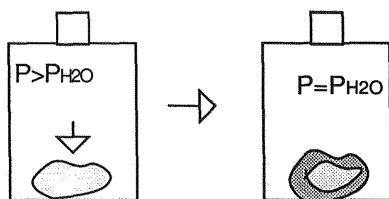


Fig. 15.6 Behavior of a compound placed in a bottle with a water vapor pressure higher than the critical. Moisture will condense on the solid, some of which will dissolve, and this process will go on until the second situation occurs, in which the vapor pressure over the solid is exactly the critical vapor pressure. If the ratio of headspace to solid is very large, and the pressure is higher than the critical, then all of the drug may dissolve, and water condense until the equilibrium pressure establishes.

solid and dissolve solid. This, in turn, will cause the vapor pressure to drop, and when a sufficient amount of water has condensed and formed saturated solution to lower the pressure above the "solid" to exactly the equilibrium pressure of the saturated solution (i.e., the critical water vapor pressure), then equilibrium has been reached.

The higher the atmospheric water vapor pressure P is, the larger is the volume V of the saturated solution formed from the solid, and the smaller is the amount of actual solid left undissolved.

Phenobarbital when it decomposes at 80°C in the presence of phosphate buffer at pH 6.7 is an example for which, in the initial stages of decomposition, this holds (Gerhardt 1989). Another example is that reported by Morris (1990) and Morris and Carstensen (1990a,b).

A situation, such as depicted in Fig. 15.1(c) is akin to a suspension. It is assumed that the decomposition is accounted for solely by the amount of material dissolved. If the saturated solution phase has a volume of V , and the drug a solubility of S , then first-order conditions prevail in the solution; that is,

$$dC/dt = -k_1 C \quad (15.5)$$

where C is concentration or, expressed as amount M , decomposed

$$VdC/dt = dM/dt = -k_1 VC \quad (15.6)$$

However, since the solution is saturated, and is assumed to remain saturated, $C = S$, so that

$$-dM/dt = k_1 VS \quad (15.7a)$$

that is, the decomposition is pseudo-zero-order, with a slope equal to the pseudo-zero-order rate constant k_0 , given by

$$k_0 = k_1 VS \quad (15.7b)$$

in other words,

$$M = M_0 - (k_1 VS)t \quad (15.8)$$

That this applies is shown in work by Morris (1990) and Carstensen and Morris (1990a,b), shown in Fig. 15.7

To quantitatively assess the decomposition, one must know k_1 , V , and S , and this should permit elucidation of the mechanism. This often holds true (Pothisiri, 1974; Pothisiri and Carstensen, 1975), but it has also been known to fail (e.g., Janahsouz et al., 1990).

In this moisture region the moisture acts as a solution layer, and degradation compounds (a) increase or decrease the drug solubility, (b) increase or decrease the kinetic parameter values of the drug, and (c) (noting that the degradants are solutes) cause a decrease in the water vapor pressure with which the moisture layer is in contact so that, in this manner, the vapor pressure relation is not violated. Gerhardt (1990) and Gerhardt and Carstensen (1989) have demonstrated that kinetic salt effects and salting-in of the drug into the moisture layer can explain the decomposition profiles exhibited by phenobarbital when moisture and buffers are present.

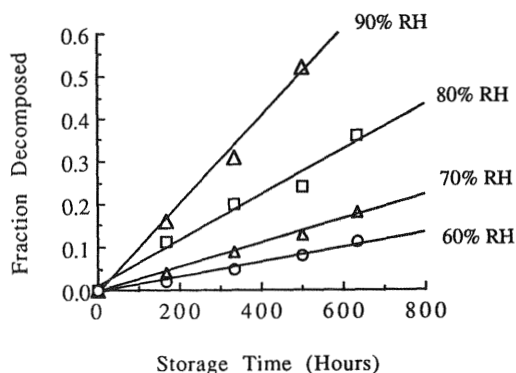


Fig. 15.7 Indomethacin decomposition at 115°C. Samples were prepared by adding microamounts of water to solid indomethacin in ampuls that were then sealed. The headspace of the ampuls was known and water amounts added were such that given water vapor pressures were obtained when the sample was heated to 115°C. This decomposition follows zero-order kinetics at the onset. (Data from Morris, 1990; and Morris and Carstensen, 1990a,b.)

Carstensen and Pothisiri (1975) and Wright and Carstensen (1986) have done likewise.

For very soluble drugs (e.g., ranitidine; Franchini and Carstensen, 1995; Carstensen and Franchini, 1995) the amount of moisture that is necessary to reach the critical relative humidity (CRH) is small (i.e., the water activity $[RH/100]$ over a saturated solution is of low magnitude). On the other hand it is high for poorly soluble drugs.

The problem here is, for quantitative assessment, to gauge the value of V .

15.6. BOUND WATER

The concept of bound water is one for which it is assumed that in a solid or a solid dosage form a certain amount of water will not affect the stability. In the previous sections, instability as a function of moisture content has been described, but of these, it is the situation at the critical moisture content that is by far the most severe. The decomposition is zero-order, and the larger the amount of water, the more unstable the compound. Indeed the zero-order rate constant increases linearly with amount of water in the system.

Figure 15.8 presents data from the work of Gerhardt (1989) and Gerhardt and Carstensen (1989). The rate constants are pseudo-zero-order and are plotted versus moisture levels. It is noted that the intercepts are nonzero, as opposed to the requirement of Eq. (15.8); that is,

$$k_0 = k_1 S[V - w^*] \quad (15.9)$$

w^* is often called kinetically unavailable moisture or *bound water*. This is true in many solid-state reactions. The bound moisture, at times, is water of crystallization. For *d,l*-calcium leucovorin (Nikfar et al., 1990a,b), there are intermittent plateaus that correspond to a constant water activity ($RH/100$) for a series of water contents (i.e., akin to a salt pair); $[V - w^*]$ is denoted kinetically available, or more simply *available moisture*.

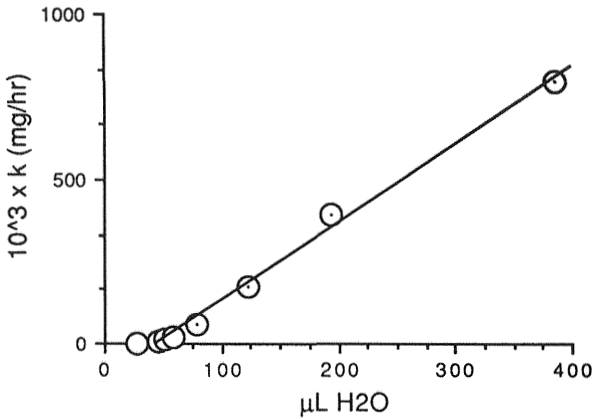


Fig. 15.8 Rate constants (pseudo-zero-order) from plots such as shown in Fig. 15.7, graphed versus added moisture. (Data from Gerhardt, 1989; Gerhardt and Carstensen, 1989.)

15.7. EXCESS WATER

The situation in Fig. 15.1d (i.e., where the amount of water suffices to bring all of the drug into solution) is denoted excess water. This may not be applicable initially in drug dosage forms, but becomes the situation as the amount of parent drug decreases in time.

Examples of this are the work by Morris (1990) in which the indomethacin/water system was studied in a closed system at 130°C (Fig. 15.9). After a short time period a eutectic consisting of indomethacin, decomposition products, and water is formed, and from this point in time the decomposition is first-order as expected for solution kinetics. The amount of time (t') required for the eutectic to form (for the mass to form a homogeneous liquid) is linear in water activity ($a = RH/100$); that is,

$$t' = \beta - q'a \tag{15.10}$$

where β and q' are constants (Fig. 15.10).

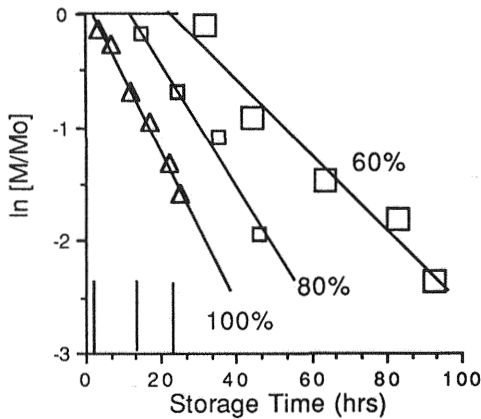


Fig. 15.9 Decomposition of indomethacin in the presence of moisture at 130°C. Data from Morris, 1990.)

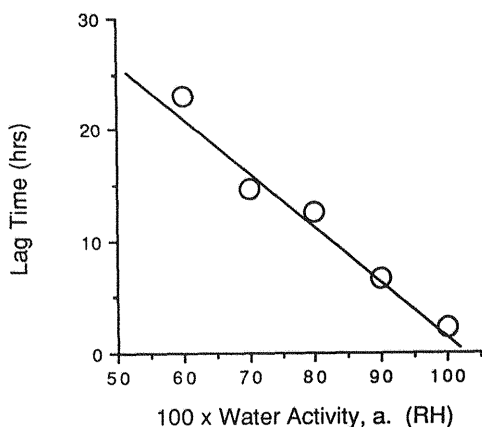


Fig. 15.10 Lag times from Fig. 15.9 plotted versus relative humidity. (Data from Morris, 1990.)

Yoshioka and Uchiyama (1986a,b), Carstensen et al. (1987), and Yoshioka and Carstensen (1990a,b) have reported similarly in relationship to propantheline bromide. Yoshioka and Uchiyama (1986a) showed that the mechanism changed at the *critical relative humidity* (CRH; i.e., the point where the water activity just equals that of a solution saturated in the drug) (Carstensen, 1977). If the solid is placed at constant relative humidity at values higher than the CRH, then the degradation consists of (a) dissolution up to where dissolution is complete, after which (b) moisture condensation will continue until a concentration of the totally dissolved drug equals that of the RH of the atmosphere.

15.8. MICROENVIRONMENTAL pH

If a formulator is aware that a compound is more stable in an acid than in a neutral or basic environment he or she may often formulate it with solid acids (e.g., citric acid) or, conversely, if it is acid-sensitive, he or she may employ bases (e.g., sodium carbonates) in an attempt to make an adjustment of “the microenvironmental pH.” In the area shown as Fig. 15.1c and d, one may, meaningfully, “buffer” a solid dosage form. Nikfar (1990), Gerhardt (1989) and Gerhardt and Carstensen (1989) have demonstrated the existence of a “solid pH-profile” that parallels (but is not identical with) the traditional pH profiles of the drug in solution (Fig. 15.11). This is another piece of evidence of the sorbed moisture layer having solvent properties.

But how does one define the microenvironmental pH? This question is not yet fully resolved. The shift in position of the kinetic pH profile in solution from the values obtained from solid-state decomposition may be attributed to the fact that one assumes that the pH value of a saturated buffer solution is the same pH used for graphing of data from the moist solid. But the sorbed solution could be of a pH value that is displaced from that observed in solution.

There is also the possibility of a kinetic salt effect. It is seen from Fig. 15.11 (Nikfar, 1990; Nikfar et al., 1990a,b) that a displacement of 1.4 pH units applies to the rate constants in the solid state. The displaced values are symbolized by squares

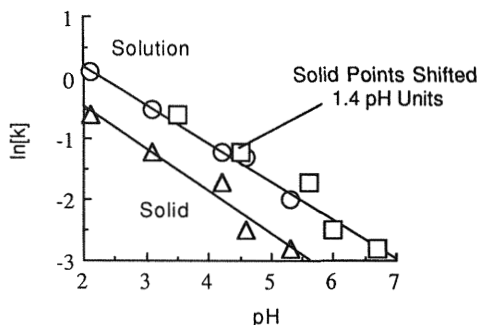


Fig. 15.11 pH rate profile of first-order rate constants extracted from kinetics of decomposition of *d,l*-calcium leucovorin. The squares are points from solid-state decomposition shifted by 1.4 pH units. (Data from Nikfar, 1992.)

in Fig. 15.11 and if such a shift is made, then the data in solution would coincide with those in the solid state. In the work published by Gerhardt (1990) it would be necessary to force a 6-pH-unit shift to obtain coincidence, so there are still unexplained factors at work.

15.9. HYDRATE-FORMING DRUGS

In considering the situation in Fig. 15.1, the adsorption isotherm is what governs the type and amount of adsorption. An *atypical* vapor/moisture curve for a salt pair is shown in Fig. 15.12. The point is that, in contrast with the general description of salt pairs, the “horizontal” lines are not really horizontal (e.g., the line FG which is the RH range in which the anhydrate is stable, actually is part of an adsorption isotherm). The same holds true for the line HJ which is usually a horizontal depicting the 0/*x* hydrate salt pair. Point J is the point that corresponds with Fig. 15.1c, and the portion KL corresponds with Fig. 15.1d.

If one now started with a crystalline anhydrate, and checked the stability of it as a function of moisture, one would truly obtain a line that would increase ever so slightly. This corresponds to the “horizontal” line at low moisture content in

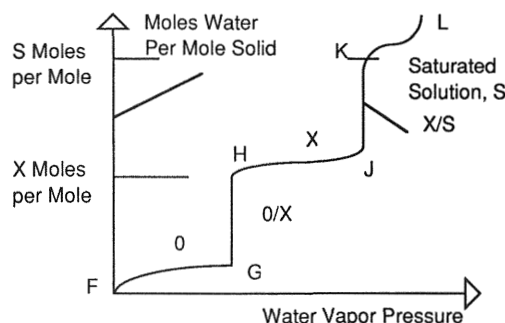


Fig. 15.12 Pressure/adsorption diagram for a salt pair. The ordinate is moles of water per mole of solid.

Fig. 15.12. Beyond this point the salt pair forms, and this has another stability profile. An example of this is amoxicillin which, if the anhydrate were crystalline to start with, would have an increasing rate constant for RH values between 0 and about 30% (the equilibrium water vapor pressure for the trihydrate). At this point, additional water will simply convert the anhydrate to trihydrate, and on completion of this, the rate constant would be that for trihydrate without adsorbed moisture. (This happens to be the maximum stability point.)

There would (might) be a small residual rate constant at 0% of moisture adsorbed. After that, as the RH is raised, BET adsorption takes place, giving rise to the line FG in Fig. 15.13, and therefore, the rate constant increases *slightly*. However, experimentally, this increase is often not great. For amoxicillin the trihydrate without adsorbed water is the maximum stability situation. Between G and H moisture is *absorbed* to form the trihydrate, and at point H this conversion is complete, giving the smallest k_0 value. For hydrates, in general, the line GH can go either up or down. Between H and J, surface adsorption on the trihydrate increases the rate constant, and at J the critical RH is encountered, and the trihydrate will start forming a saturated solution. More and more bulk saturated solution will form, increasing the rate constant from J to K. After this unsaturated solutions form and the *decomposition rate* (not the rate constant) increases because the water volume term increases.

In the case of amoxicillin and other β -lactams, the anhydrate formed by dehydration of the tri- (or higher) hydrate is amorphous, and in this example the line FG has a steep positive slope because the amorphous anhydrate would be much more unstable than the crystalline form.

15.10. PRESENCE OF BUFFERS

If hydrate-forming buffers are present, there will be given relative humidities for which one salt form reverts to another, and in these regions, more water added to the system will not change the rate constant, for the water is consumed by the buffer. Nikfar (1990) has shown this in a situation in which calcium leucovorin in the presence of sodium citrate and citric acid had a given RH value for several moisture contents, and rate constants that were constant at these various moisture contents.

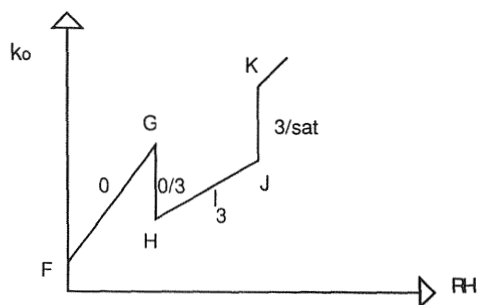


Fig. 15.13 Exaggerated schematic of rate constants as a function of RH for a compound forming a trihydrate.

Often hydrates are added to drug substances that are hydrates and are most stable as hydrate. Cephalosporins are often pentahydrates, and if formulated with Trona (approximate formula $\text{Na}_2\text{CO}_3 \cdot 2\text{NaHCO}_3 \cdot 24\text{H}_2\text{O}$), the antibiotic will remain in its pentahydrate form because the salt pair RH range for Trona encompasses that of the cephalosporin. The value of k_0 will, therefore, always be dictated by the RH of the salt pair range of the Trona (i.e., be at a given RH); therefore, it will not change (unless moisture conditions completely dehydrate or deliquesce the Trona). The RH range of a salt pair, however, decreases with increasing temperature, and at a given temperature (as covered elsewhere) becomes zero. This is the critical temperature for the hydrate.

Accelerated tests, therefore, must be carried out with control of RH so that the integrity of the hydrate (e.g., the pentahydrate in the case of streptomycins) is maintained.

SYMBOLS

- A^* = concentration of active sites
- a = water activity (RH/100)
- BET = Brunauer–Emmett–Teller isotherm
- C = concentration of drug in bulk layer
- $[\text{H}_2\text{O}]$ = water concentration on surface
- k = rate constant
- k_1 = first-order rate constant
- k_0 = pseudo-zero-order rate constant
- $k' = k[\text{H}_2\text{O}]$
- M = mass of intact drug
- Q = heat of fusion
- q' = constant (in lag time equation)
- RH = relative humidity
- S = solubility
- T_d = testing temperature, K
- T_m = melting point, K
- t = time
- $t_{1/2}$ = half-life
- t' = lag time
- V = volume of saturated bulk layer
- w^* = mass or volume of “bound” water
- x = fraction decomposed
- β = constant (in lag time equation)

REFERENCES

- Attarchi F (1984). PhD dissertation. Decomposition of aspirin in the moist solid state. School of Pharmacy, University of Wisconsin, Madison, WI.
- Bawn C (1955). In: W Garner, ed. Chemistry of the Solid State. Academic Press, New York, p 254.
- Carstensen JT (1977). Pharmaceutics of Solids and Solid Dosage Forms. John Wiley & Sons, New York, p 12.

- Carstensen JT, Attarchi F (1988). J Pharm Sci 77:318.
- Carstensen JT, Franchini M (1995). Drug Dev Ind Pharm 21:523.
- Carstensen JT, Li Wan Po A (1993). Int J Pharm 83:87.
- Carstensen JT, Pothisiri P (1975). J Pharm Sci 64:7.
- Carstensen JT, Van Scoik K (1990). Pharm Res 7:278.
- Carstensen JT, Danjo K, Yoshioka S, Uchiyama M (1987). J Pharm Sci 76:548.
- Franchini M, Carstensen JT (1994). Pharm Res 11:S238.
- Gerhardt A (1990). PhD dissertation. Decomposition of Phenobarbital in the Solid State. School of Pharmacy, University of Wisconsin, Madison, WI, p 61.
- Gerhardt A, Carstensen JT (1989). Pharm Res 6:S142.
- Gluzman M (1954). Uch Zap Khar'kov Univ 54; Tr Khim Fak Nauch-Issledovatel Inst Khim 12:333.
- Gluzman M (1956). Tr Khim Fak Nauch-Issledovatel Inst Khim 14:197.
- Gluzman M (1958). Z Fiz Khim 32:388.
- Gluzman M, Arlozorov D (1957). Z Fiz Khim 31:657.
- Guillory K, Higuchi T (1962). J Pharm Sci 51:100.
- Hollenbeck RG, Peck GE, Kildsig DO (1978). J Pharm Sci 67:599.
- Janahsouz H, Waugh W, Stella V (1990). Pharm Res 7:S195.
- Kornblum S, Sciarrone B (1964). J Pharm Sci 53:935.
- Leeson L, Mattocks A (1958). J Am Pharm Assoc Sci Ed 47:329.
- Li Wan Po A, Mroso PV (1984). Int J Pharm 18:287.
- Marshall K, Sixsmith D, Stanley-Wood NG (1972). J Pharm Pharmacol 24:138.
- Morris T (1990). PhD dissertation. Decomposition of indomethacin in the solid state. School of Pharmacy, University of Wisconsin, Madison, WI.
- Morris T, Carstensen JT (1990a). Pharm Res 7:S195.
- Morris T, Carstensen JT (1990b). Pharm Res 7:S196.
- Mroso PV, Li Wan Po A, Irwin WJ (1982). J Pharm Sci 71:1096.
- Nikfar F (1990). PhD dissertation. Decomposition of *dl*-calcium leucovorin in the solid state. School of Pharmacy, University of Wisconsin, Madison, WI.
- Nikfar F, Ku S, Mooney KG, Carstensen JT (1990a). Pharm Res 7:S127.
- Nikfar F, Forbes SJ, Mooney KG, Carstensen JT (1990b). Pharm Res 7:S195.
- Pikal MJ, Lukes AL, Jang JE (1977). J Pharm Sci 66:1312.
- Pothisiri P (1975). PhD dissertation. Decomposition of *p*-aminosalicylic acid in the solid state. School of Pharmacy, University of Wisconsin, Madison, WI.
- Pothisiri P, Carstensen JT (1975). J Pharm Sci 64:1931.
- Prout EG, Tompkins FC (1944). Trans Faraday Soc 40:489.
- Wright JL, Carstensen JT (1986). J Pharm Sci 75:546.
- Yoshioka S, Carstensen JT (1990a). J Pharm Sci 79:799.
- Yoshioka S, Carstensen JT (1990b). J Pharm Sci 79:943.
- Yoshioka S, Uchiyama M (1986a). J Pharm Sci 75:92.
- Yoshioka S, Uchiyama M (1986b). J Pharm Sci 75:459.

This Page Intentionally Left Blank

16

Apparent Volumes and Densities

16.1. Density and Porosity Definitions	282
16.2. Correlation Between Density and Porosity	282
16.3. Apparent Densities of Binary Mixtures	283
16.4. Closest Packing	285
16.5. The Wall Effect	286
16.6. Stable Configurations	288
16.7. Characteristics of Mixtures of Spheres	288
16.8. Wall Effect for Spheres	290
16.9. Application to Real Powders	291
16.10. Porosities of Mixtures of Several Particle Size Cuts	291
16.11. Compaction from Vibration and Tapping	295
Symbols	296
References	297

A compact solid (e.g., a crystal) has a fairly well-defined “density,” in that this term implies the weight of the substance per real volume. Hence, it has the dimension of mass per volume (g/cm^3). When dealing with particulates, however, the volume V (of a drum, for instance) is partly occupied by solid particles, and partly by void space. Hence, if the mass M of powder in the drum is determined by weighing, then the ratio:

$$\rho' = M/V \quad (16.1)$$

is a “density term.” It is obviously smaller than the “true” density (e.g., of a crystal, or the particles from which the powder is made up), and ρ' is referred to as *apparent density* or *bulk density*.

The importance of apparent density in pharmaceutical operations is obvious. The amount of powder that will theoretically fit in a capsule or in a tablet die or punch volume is determined by this parameter, the number of capsules or tablets or the amount of bulk powder that will fit in a drum are examples for which the apparent density is performance-controlling.

16.1. DENSITY AND POROSITY DEFINITIONS

A perfect crystal would have a density determined by the crystallographic system and by the molecular weight of the substance. This is referred to as the *molecular density* in the following. As mentioned in earlier chapters, real crystals have defects and flaws, and the actual density, therefore is somewhat smaller and is referred to as the *crystallographic density*. Whereas the molecular density is a given number, the crystallographic density may vary ever so little, depending on defect concentration, but these differences will mostly be small, and the two terms are usually almost equal.

Granules are often produced in pharmaceuticals, and these are aggregates of crystals and contain a certain fraction, ε_p , void space. This is referred to as the *particle porosity*, and the density ρ_p is referred to as the *particle density*.

If a particulate powder is poured into a container, as mentioned in the introduction, then it will achieve a certain *cascaded apparent density* ρ' , and an associated *bed porosity* ε' , and if it is then “tapped” in a reproducible fashion, it will reduce in volume and attain a somewhat higher *tapped density*, ρ'_{tap} , and an associated *tapped bed porosity*, $\varepsilon'_{\text{tap}}$.

16.2. CORRELATION BETWEEN DENSITY AND POROSITY

Assume a cylinder, such as shown in Fig. 16.1, with volume V . Powder is transferred to the cylinder, and the volume of the powder is V_s . The fraction of the volume that is occupied by solid is, then:

$$v_s = V_s/V \quad (16.2)$$

where v_s is known as the *solids fraction*.

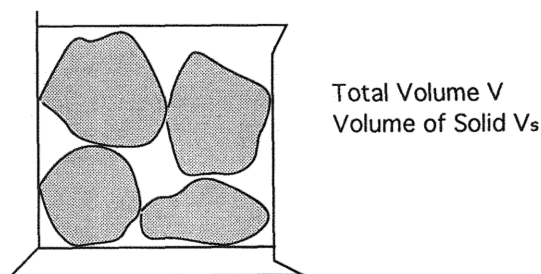


Fig. 16.1 Schematic for definition of fractional volume and apparent density.

The part that is *not* solid in the volume V is denoted the *void space*, and the *porosity* ε is defined as the fraction of the volume that is void space; that is,

$$\varepsilon = 1 - v_s \quad (16.3)$$

This, hence, is the void space in a volume of 1 cm^3 with solids fraction v_s . The mass (weight) of this unit volume would be the apparent density.

$$\rho' = v_s \rho \quad \text{or} \quad v_s = \rho' / \rho \quad (16.4)$$

Introducing this into Eq. (16.3) yields the oft-used equation

$$\varepsilon = 1 = (\rho' / \rho) \quad (16.5)$$

16.3. APPARENT DENSITIES OF BINARY MIXTURES

Next, attention is directed toward the apparent densities of mixtures of two powders. The situation is that the material in Fig. 16.1 is considered to be the coarse portion of a mixture of a coarse and a fine powder. It is assumed that the fine powder can *percolate* (i.e., that the small particles “fit” into the interstices of the coarse fraction). The apparent density of the coarse powder is denoted ρ'_c (g/cm^3) and its particle density is denoted ρ_c . For simplicity (without losing generality) it is assumed that the graduate has a volume of 1.0 cm^3 . The weight of the contents is, obviously ρ_c .

If fine, percolating powder (of apparent density ρ_f) is added to the cylinder (Fig. 16.2a), then it will fit in the void space, until the void space is filled up. The total volume is 1 cm^3 , so the volume of the void space is ε_c . Before the addition of the fine powder, the mass of powder in the 1.0 cm^3 is ρ_c . When m grams of B are added, then the density is

$$\rho = \rho_c + m \quad (16.6)$$

since the volume has not increased. The fraction of fines is

$$x = m / (\rho_c + m) \quad (16.7)$$

that is,

$$m = x \rho_c / (1 - x) \quad (16.8)$$

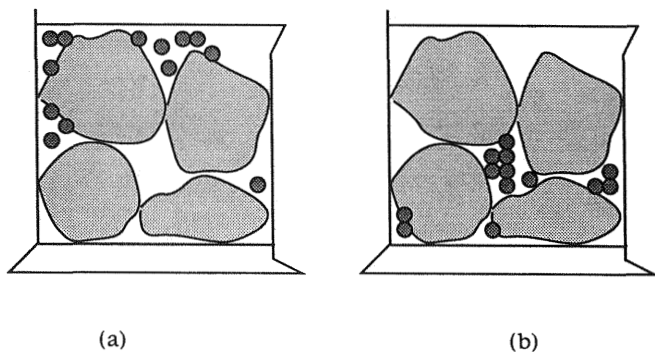


Fig. 16.2 Schematic of adding fines to 1 cm^3 of coarse material.

But the mass (weight) of the contents of the cylinder is equal to the apparent density, ρ' , so that

$$\rho' = \rho_c + m = \rho_c \{1/(1-x)\} \quad (16.9)$$

or

$$1/\rho' = (1/\rho_c)\{1-x\} \quad (16.10)$$

This equation holds up to the point of maximum apparent density (minimum apparent volume). At the point of maximum density, the weight of fine material is the volume it occupies $\{\varepsilon_c\}$, times its apparent density ρ'_f (Fig. 16.3). Hence, the maximum apparent density of the mixture is

$$\rho'_{\max} = \rho'_c + \varepsilon_c \rho'_f \quad (16.11)$$

When $x > x_{\max}$ then the coarser particles are simply scattered in a bed of the fine particles; 1 g of mixture now contains a mass (weight) of $1-x$ of coarser material and a mass (weight) of x , of fine material. The volume $v_{\max}$, occupied by this is $(1-x)/\rho_{pc}$, where ρ_{pc} is the particle density of the coarse fraction, plus x/ρ'_f . Hence,

$$v_{\max} = (x/\rho'_f) + (1-x)/\rho_{pc} = \{(\rho_{pc} - \rho'_f)/(\rho'_f \rho_{pc})x\} + (1/\rho_{pc}) \quad (16.12)$$

The volume of 1 g of mix (cm^3/g) is, however, the reciprocal of the apparent density of the mix (g/cm^3), so that

$$1/\rho'_{\max} = \{(\rho_{pc} - \rho'_f)/(\rho'_f \rho_{pc})x\} + (1/\rho_{pc}) \quad (16.13)$$

This is a straight line with $x=0$ intercept of $(1/\rho_{pc})$ and intersecting the $x=1$ ordinate axis at $(\rho_{pc} - \rho'_f)/(\rho'_f \rho_{pc})$. To the left of the maximum apparent density [see Eq. (16.10)]

$$1/\rho' = \rho_c + m = (1-x)/\rho_c \quad (16.14)$$

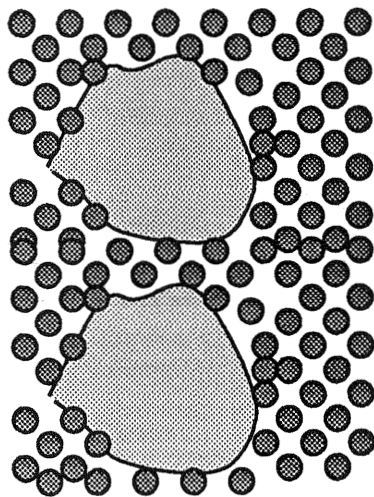


Fig. 16.3 Schematic of arrangement beyond the point of maximum density.

so that here the reciprocal of the apparent density will be a straight line intersecting the $x = 0$ ordinate axis at $1/\rho_c$ and the $x = 1$ ordinate axis at zero. Hence, this would suggest a linear relation, as shown in Fig 16.4.

The actual apparent density will be a function of fines fraction as shown in Fig. 16.5. The relations have been borne out, experimentally (Ben-Aim and LeGoff, 1967, 1968; Carstensen et al., 1978a), in the sense that linearity of apparent volumes with fines fraction holds on either side of the maximum density, but the intercepts of the apparent volume plots fail to have the theoretical values. This is attributed to "wall effects," a subject that will be discussed forthwith.

16.4. CLOSEST PACKING

Whether tapping produces a closest packing or not is open to debate and is probably a function of the shape factor of the particles in question.

By way of Rogers' theorem (Rogers, 1958), the closest a packing of monodisperse spheres can attain is

$$1 - \{3\sqrt{2}[\cos^{-1}(1/3) - (\pi/3)]\} = 0.2204 \quad (16.15)$$

but, according to Rocke (1970/71) the lowest experimentally determined fraction has been found to be

$$1 - \{\pi/(3\sqrt{2})\} = 0.26 \quad (16.16)$$

This is a rhombohedral-ordered packing, also known as face-centered cubic or hexagonal close-packed.

Packing patterns in tapped density depictions are usually considered tetrahedral, but Berg et al. (1970/71) have reported this to be layers of hexagonal close-packed structure.

These authors have shown experimentally, that the traditional "one-dimensional" tapping does not produce the closest packing; a random shaking is necessary to obtain this.

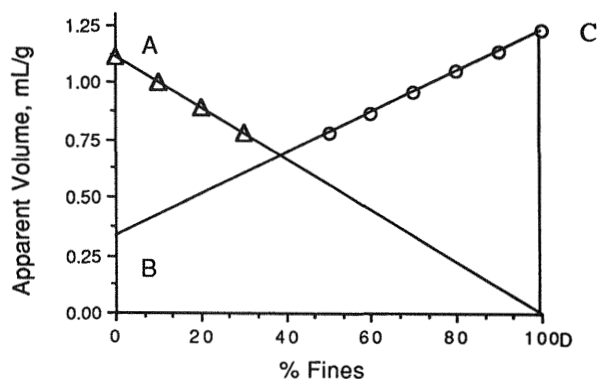


Fig. 16.4 Linear relation of specific apparent volume as a function of fraction (or percent) of fines. Least-squares fit lines are $y = 0.33 + 0.009x$ for x values above the minimum and $y = 1.11 - 0.011x$ for x values below the minimum.

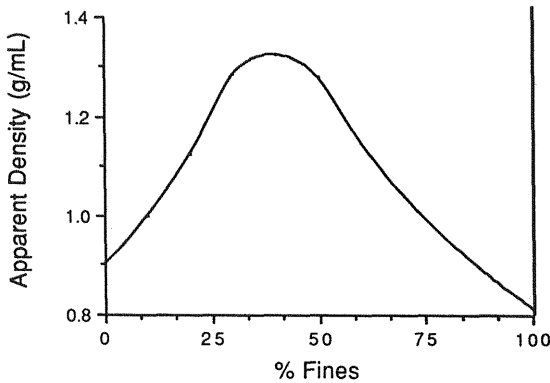


Fig. 16.5 Apparent density data corresponding to the data in Fig. 16.4.

Carstensen (1980) and Carstensen and Chan (1976) have reported on the porosity of conical heaps of spheres (encountered in repose angle measurements) and found a limiting porosity of 0.38 in such an arrangement.

One variable that governs ρ' is, intuitively, the particle size (diameter, d), and (less intuitively) the container diameter (D) and the mode of compaction. The dimensionless parameter $a = d/D$ (the reduced particle size) is often employed.

Rocke (1970/71) showed that when monodisperse spheres are deposited in a cylindrical container, then the relative mean spacing h between layers is not affected by the reduced particle size. This author also showed that, for spheres, the porosity ϵ , decreases to a limiting value, or 0.29, assuming layers to be arranged hexagonally. Kelly (1970/71) has reported on packing of a second layer placed on a base layer, and has used probability theory to arrive at packing schemes, but the important facet is essentially the finding by Rocke (1970/71) that the interlayer distance h is not affected by the reduced particle size.

Berg et al. (1969/70) derived a theory whereby the apparent density ρ' , should be proportional to $1/d$ in a given vessel. They treated data published by Roller (1930), by an inverse particle diameter plot.

For real powders, the assumption of sphericity is overly simple. The effect of particle shapes has been reported by Ridgway and Rupp (1969) and by Pitkin and Carstensen (1990).

Rocke (1970/71) found the relative mean spacing (h/d) to be independent of the reduced diameter (d/D), and to have a value of 0.88; that is,

$$h/d = 0.88 \, d/D \tag{16.17}$$

16.5. THE WALL EFFECT

Because a pharmaceutical powder is not spherical (the closest to spherical being wet granulated granules), a simpler, but more realistic, mode of viewing the situation would be the following.

If it is assumed, as schematized in Fig. 16.6, that the bed has an apparent density of ρ'_1 at infinite bed diameter, then, if it is confined to a cylinder of diameter

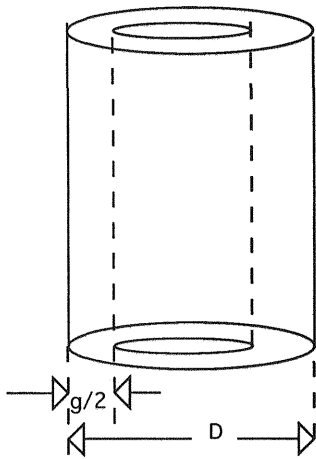


Fig. 16.6 Schematic of calculation of wall effect on overall apparent density of particles placed in a cylinder with height H (cm). Wall effects are felt a distance of $g/2$ (cm) into the bed.

D and height H , will there be a wall effect at the wall and penetrating a certain distance, $g/2$, from the wall into the powder bed. This conforms with the model proposed by Ridgway and Tarbuck (1966) except the wall effect is only assumed to reach out one “wavelength.”

Reference is made to Fig. 16.6. The effective depth (thickness), $g/2$, of the wall effect is a function of the diameter of the particle and is assumed to be of the form:

$$g = \beta d \quad (16.18)$$

where β is a constant, depending on the material. There are therefore two parts to the powder bed, the inner cylinder of diameter $D - g$ where the apparent density will be ρ'_1 and the outer cylindrical shell of thickness $g/2$, where the apparent density will be ρ'_2 . The weight (mass) of powder with density ρ'_1 is, therefore,

$$\text{Mass of outer cylinder: } (\pi/4)(D - g)^2 H \rho'_1 \quad (16.19)$$

and similarly the mass (grams) of powder with density ρ'_2 is

$$\text{Mass of outer shell: } [(\pi/4)H\{(D^2) - (D - g)^2\}]\rho'_2 \quad (16.20)$$

The total mass (weight) M is the sum of these two terms. Because the total volume V is $(\pi/4)(D^2 H)$ it follows that the apparent density is

$$\begin{aligned} \rho' &= M/V = \{1 - (1 - g/D)^2\}\rho'_2 + \{1 - (g/D)\}^2\rho_1 \\ &= \{1 - (1 - \beta d/D)^2\}\rho'_2 + \{1 - (\beta d/D)\}^2\rho_1 \end{aligned} \quad (16.21)$$

Data are generated using $\beta = 1.0$, $d = 0.5$, $\rho_1 = 0.8$, $\rho_2 = 0.3$, as an example, and are shown in Fig. 16.7.

From the model, the limiting apparent density (at infinite container diameter) should be $\rho_1 = 0.8$, and the graph bears this out. The shape of the curve in Fig. 16.7 is comparable with that found by Berg et al. (1969/70), who investigated apparent densities of Portland cement and calcium sulfate hemihydrate. They found that with

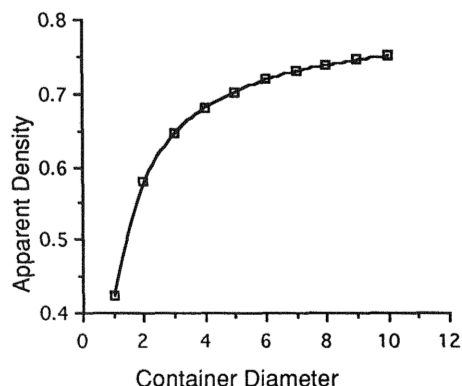


Fig. 16.7 Graph plotted according to Eq. (16.21) using $\beta = 1.0$, $d = 0.5$, $\rho_1 = 0.8$, $\rho_2 = 0.3$.

increasing container diameter D , the apparent density would increase asymptotically to a limiting value, and they found that at these values, $\varepsilon = 0.395$ for Portland cement and 0.48 for calcium sulfate hemihydrate.

16.6. STABLE CONFIGURATIONS

It is apparent that the cascaded density is not a stable configuration, but surprisingly, it is quite reproducible. The tapped density, depending on the method for tapping, is also fairly reproducible, but in accordance with the previous section is not necessarily the closest packing.

If one considers the situation in Fig. 16.2 it is obvious that if the fine powder is cascaded into the coarse powder, it may temporarily “lie on top of it,” but eventually would settle down. Hence, the bed would not be uniform (see Fig. 16.2b). It is only when one has arrived at the maximum density that stability is imparted.

Blending efficiencies will be a subject of a subsequent chapter, but provided there are no significant forces between the particles (that cohesion or electrostatic forces are not at play), the maximum density configuration is the only stable one. Frequently, when one powder component is much larger than others (e.g., vitamin A beadlets in vitamin formulations) the coarser particles will seem “to rise to the top.” What essentially happens is that the finer particles sift to the bottom.

It could be possible to continue the argument, using a third fraction of even finer particles that would fit into the interstices of the binary mixture, and to arrive at some sort of correlation between particle size distribution and stability of the powder. This will be covered in a subsequent section.

16.7. CHARACTERISTICS OF MIXTURES OF SPHERES

Real powders are not spheres, and various means of describing the deviation from sphericity have been discussed in previous chapters, such as the volumetric shape factor. For densities of bulk powders, the packing radius (or the sphericity) is often referred to (Fig. 16.8). It is obvious that the porosity of a packed, “real” powder sample may be less or more than that of a sphere.

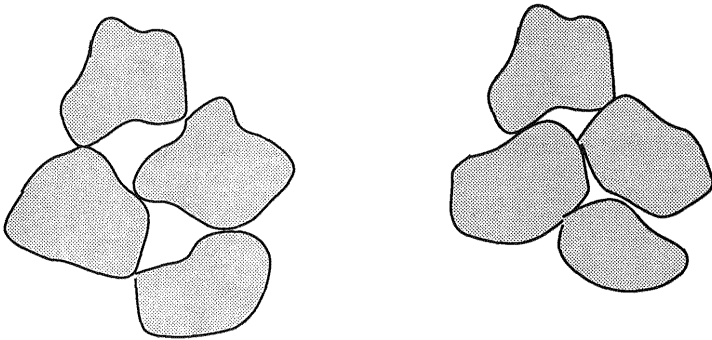


Fig. 16.8 Loose and closer packing of irregular particles.

The example in Fig. 16.2 is one for which a smaller particle is placed in the interstices of a larger particle. It should be pointed out that the considerations in Sec. 16.1 are based on a cubic arrangement, and refers simply to porosities. If packing radii are employed, then the packing of the mixture is based on the packing arrangement and on Table 16.1 (Manegold et al., 1931). For theoretical considerations, spherical approximations are often used.

If one places only one sphere in the voids between large spheres, then the maximum diameter of the small sphere is related to that of the large sphere, d_{large} , by the numbers shown in Table 16.1. With large steel spheres it has been shown (Smith et al., 1929; Smith, 1933) that the coordination number and the porosity, on the average, is a mixture of cubic and rhombohedral packings. If the fraction of the packing that is rhombohedral is denoted F_r , and that which is cubic is F_f , then

$$F_r + F_f = 1 \tag{16.22}$$

and the porosity may be expressed as

$$\varepsilon = 0.26F_r + 0.48F_f \tag{16.23}$$

The unit volume of a cubic packing is denoted unity, and that of a rhombohedral packing is $2^{-1/2}$; hence, the number of spheres in a unit volume are 1 and $2^{-1/2}$, respectively. The coordination numbers are 6 and 12 for these packing modes, so that the average coordination number for a mixture is given by

$$N = 1\{12(2^{1/2})F_f + 6F_r\}/\{2^{1/2}F_r + F_f\} \tag{16.24}$$

Table 16.1 Bed Properties When One Small Particle Is Placed in Each Void Space

Arrangement	Porosity	Diameter of the small sphere	Porosity of the mixture
Cubic	0.48	$0.72d_{\text{large}}$	0.27
Rhombohedral	0.26	$0.23d_{\text{large}}$	0.19
Orthorhombic	0.40	$0.53d_{\text{large}}$	0.31

Source: Manegold, 1936.

Combining Eqs. (16.23) and (16.24) then gives

$$\varepsilon = (0.414N - 6.53)/(0.414N - 10.97) \quad (16.25)$$

It has been shown, experimentally, that the packing density, when the particles are spherical, increases as the ratio of vessel to particle diameter increases to 10, and above this the packing density approaches 0.62 (McGeary, 1961; Leva and Grummer, 1948). Experimentally (Ridgway and Tarbuck, 1967) it has been shown for a large range of porosities that

$$\varepsilon = 12.072 - 0.119N + 0.00043N^2 \quad (16.26)$$

Most encountered porosities are between 0.25 and 0.5 and then Eq. (16.26) becomes, approximately,

$$N = 22.5 - 39.4\varepsilon \quad (16.27)$$

16.8. WALL EFFECT FOR SPHERES

As mentioned when the particles are spherical, the porosity increases as the ratio of vessel to particle diameter increases to 10, and above this the packing density approaches 0.62. The porosity, however, is not constant throughout the powder mass, as shown in Fig. 16.9. The coordination number will change if the packing changes positionally in the bed, and the numbers used are between 8 and 9, where there are 6 and 7 contacts between particles.

Figure 16.9 shows random close packing where the solids (particle) fraction is 0.62, and where the average value of N is 8.5.

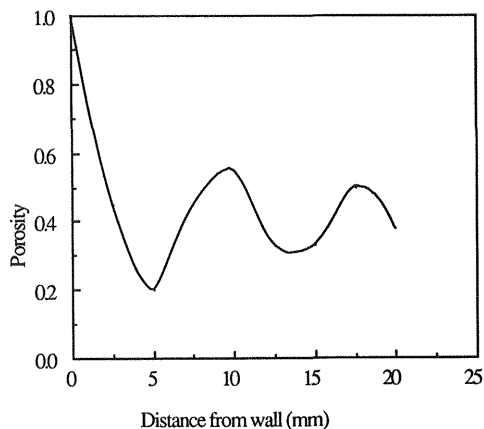


Fig. 16.9 Radial distribution of porosities of powder in a cylinder. (Data from Ridgway and Tarbuck, 1968.)

16.9. APPLICATION TO REAL POWDERS

Figure 16.9 demonstrates the point that real powders may deviate from the ideal spherical constructs described in the previous sections. The shapes of particles have been described in Chaps 4 and 5.

Figure 16.10 employs the sphericity S_e of the particles as a measure of irregularity. This, as defined by Wadell (1934) is the ratio of the external surface area of a sphere of equivalent volume to the actual surface area of the particle. This would equal 1.0 for a perfect sphere, and then decrease with increasing shape irregularity. It is seen in the figure that the following empirical relationship holds:

$$\ln[S_e - 0.1] = 0.995 - 3.292\varepsilon (R = 0.99) \quad (16.28)$$

For real powders, the traces in Fig. 16.4 retain their shape, but not their position. Figure 16.11 depicts the situation where the voids in the first component is 0.5. The size ratio between large and small particles will obviously have an effect, and as this ratio increases from 0.1 to 0.4 the curves will have the shapes shown in the figure.

The roughness of a particle also reflects the packing characteristics. This is demonstrated in Fig. 16.12. The abscissa in the figure is the coefficient of roughness divided by the particle density. The data are quite scattered, but the general trend of an increase in porosity with increasing particle roughness is apparent. Therefore, it is to be expected that additives, such as lubricants (magnesium stearate) or glidants (talc), will reduce the porosity in that they “fill out” the crevices (the roughness) of the surface.

16.10. POROSITIES OF MIXTURES OF SEVERAL PARTICLE SIZE CUTS

The foregoing discussion has concerned itself with binary mixtures, but when several mesh cuts are mixed, then even tighter packings are possible.

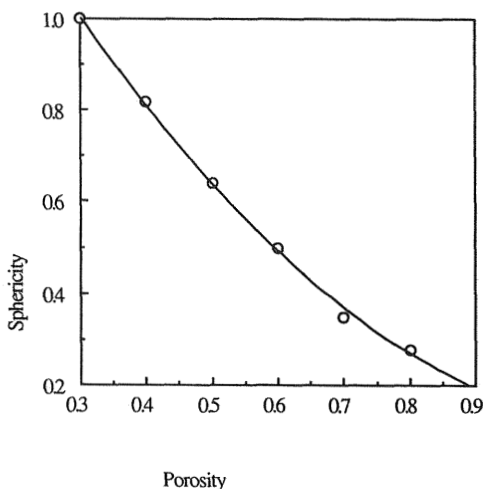


Fig. 16.10 Sphericity of particles as a measure of irregularity. (Data from Brown, 1950.)

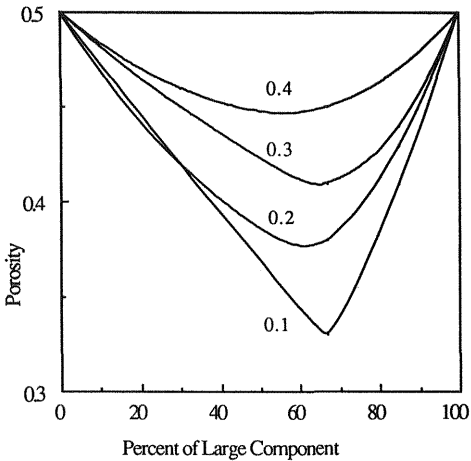


Fig. 16.11 Effect of size ratio of large to small particles on position. (Data from Furnas, 1929.)

Suppose the cavity between larger spheres in a given (e.g., rhombohedral) arrangement (the sphere size arbitrarily set at size 1.0) are filled, each with one smaller sphere, then the size of this smaller sphere can be calculated. If the (now smaller) cavities between the spheres are now filled with even smaller (tertiary) spheres, then the diameters of these may be calculated, and so on. This is denoted a Horsfield packing (Horsfield 1934; White and Walton, 1937). Characteristics of Horsfield packings are shown in Table 16.2.

It can be shown that the limiting porosity (i.e. with as many level of spheres as possible) is 0.039.

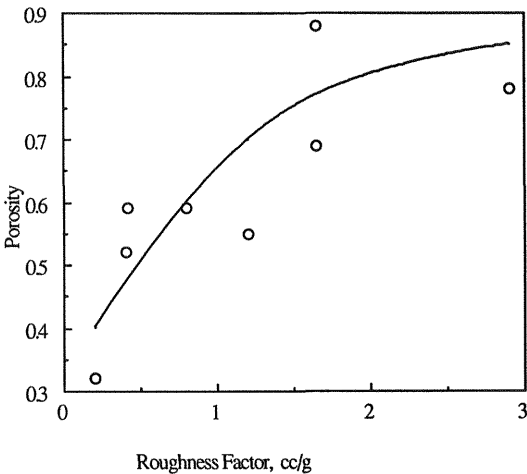


Fig. 16.12 Effects of particle roughness on packing characteristics. (Data from Crosby, 1961.)

Table 16.2 Characteristics of Horsfield Packings

Spheres	Ratio of size to primary sphere	Porosity of the mixture
Primary	1.0	0.260
Secondary	0.414	0.207
Tertiary	0.225	0.190
Quaternary	0.175	0.158

Following the development by Shinohara (1990) the volumes of each of the sphere (i.e., primary, secondary, and so on) are given by

$$V_1 = V_m(1 - \varepsilon) = f_1 \tag{16.29}$$

$$V_2 = \varepsilon V_m(1 - \varepsilon) = f_2 = (1 - f_1)\varepsilon \tag{16.30}$$

$$V_3 = \varepsilon^2 V_m(1 - \varepsilon) = f_3 = (1 - f_1)\varepsilon^2 \tag{16.31}$$

$$V_n = (1 - f_1)\varepsilon^{n-2} \tag{16.32}$$

where V_m is the unit particle volume, given by

$$V_m = 1/(1 - \varepsilon^2) \tag{16.33}$$

Summing Eqs. (16.27) to (16.30) gives the total solids volume, V_t as

$$V_t = (1 - \varepsilon^n)/(1 - \varepsilon^2)$$

Table 16.3 gives the composition when there are minimum voids.

It is instructive to examine the particle size distribution of the compositions with the minimum voids. It will later be seen, that when voids are not completely filled, then segregation *may* occur, but when they *are* filled, then there is no potential for segregation.

The data in Table 16.3 may be analyzed in light of the data in Table 16.2. If the fractions in Table 16.3 have the diameters indicated in Table 16.2 for primary, secondary, tertiary, and quaternary spheres, then the particle size can be calculated. These calculations are shown in Table 16.4 and are shown graphically in Fig. 16.13.

Although there are only three points in each distribution, Fig. 16.13 shows excellent linearity in all four cases. Normal and Weibull distributions do not give good fits.

The fact that Horsfield packings give lognormal distributions does not exclude the possibility that other distributions may also give close, nonseparable distributions, but it is one instance where *closest packings that give minimum porosity (and hence, non-segregating, highest fill into a volume (e.g., a capsule) are lognormally distributed.*

Table 16.3 Composition When There Are Minimum Voids When Four Components^a Are Present

Initial porosity in single component	Volume percent of fraction 1	Volume percent of fraction 2	Volume percent of fraction 3	Volume percent of fraction 4
0.3	70.7	21.1	6.3	1.9
0.4	61.7	24.6	9.8	3.9
0.5	53.3	26.7	13.4	6.7
0.6	46.0	27.6	16.5	9.9

^aFraction 1 is primary (coarsest), fraction 4 is finest.
Source: Furnas, 1931.

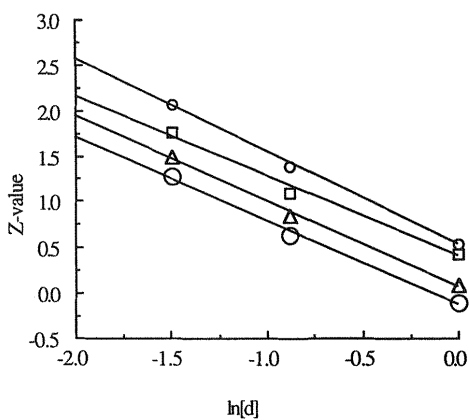


Fig. 16.13 Particle size distributions of Horsfield packings. The symbols are small circles: $\varepsilon = 0.3$, $Z = 0.5334 - 1.0197 \ln[d]$, ($R = 0.998$); squares; $\varepsilon = 0.4$, $Z = 0.4076 - 0.8752 \ln[d]$, ($R = 0.989$); triangles; $\varepsilon = 0.5$, $Z = 0.063 - 0.9420 \ln[d]$, ($R = 0.996$); large circles: $\varepsilon = 0.6$, $Z = -0.1225 - 0.9157 \ln[d]$, $R = 0.995$).

Table 16.4 Data for Distribution of Horsfield Packing

<i>d</i>	ln[<i>d</i>]	$\varepsilon = 0.3$		$\varepsilon = 0.4$		$\varepsilon = 0.5$		$\varepsilon = 0.6$	
		Cum %	$\varepsilon = 0.3$ <i>Z</i>	Cum %	$\varepsilon = 0.4$ <i>Z</i>	Cum %	$\varepsilon = 0.5$ <i>Z</i>	Cum %	$\varepsilon = 0.6$ <i>Z</i>
1.0	0	70.7	0.55	61.7	0.44	53.3	0.085	46	−0.10
0.414	−0.88	91.8	1.39	86.3	1.10	80.0	0.84	73.6	0.63
0.225	−1.53	98.1	2.08	96.1	1.76	93.3	1.50	90.1	1.276
0.176	−2.08	100		100		100		100	

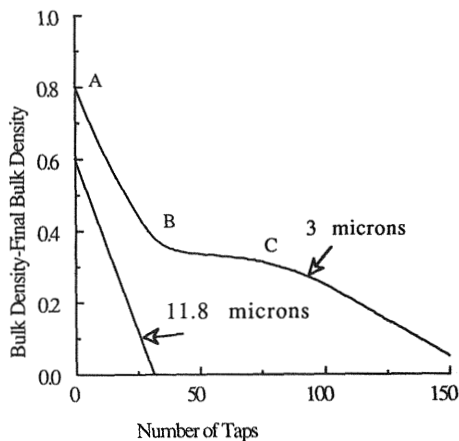


Fig. 16.14 Consolidation kinetics of white alundum. (Data from Arakawa et al., 1966.)

16.10. COMPACTION FROM VIBRATION AND TAPPING

The apparent densities referred to in the foregoing are what is known as cascaded apparent densities (i.e., the density that is obtained by pouring powder into, e.g., a graduated cylinder). When such a cylinder is tapped, the powder will *consolidate* or *compact*. If ρ'_{tap} is the tapped density (i.e., the apparent density after an large number of taps), ρ' is the cascaded apparent density, and ρ'_n is the apparent density after n taps, then it can be shown, experimentally (Kuno, 1956) that

$$\rho'_n - \rho' = (\rho'_{\text{tap}} - \rho') \exp(-kn) \quad (16.34)$$

It is noted, from Fig. 16.14, that there are “nicks” in the curves (e.g., at points B and C) in the curve for the 3- μm powder. Each of the segments AB, BC, and the line beyond C are quite linear, but the basic process must be different. This often occurs with very fine powders. All of the foregoing considerations have been based on the assumption of noncohesion, and when powders are cohesive—and this, as we shall see in subsequent chapters, often occurs with fine powders—then agglomerates may form, and the break in the curves may be due to breakage of agglomerates. The breaks in Fig. 16.14 show in particles that are 3 μm in size, but not in particles that are 11.8 μm in size

When a powder is vibrated, then compaction takes on different kinetics, and Fig. 16.15 shows that the packing density goes through a maximum when packing density ρ , is plotted versus vibrational density G , given by

$$G = a(2\pi\Omega)^2/g \quad (16.35)$$

where a is a constant, Ω is the amplitude, and g is gravitational acceleration.

The curves, as shown in the figure, are often parabolic.

$$y = 0.42388 + 0.11403x - 2.1600e-2x^2 \quad R^2 = 0.932 \quad \bigcirc \text{ Bulk Density}$$

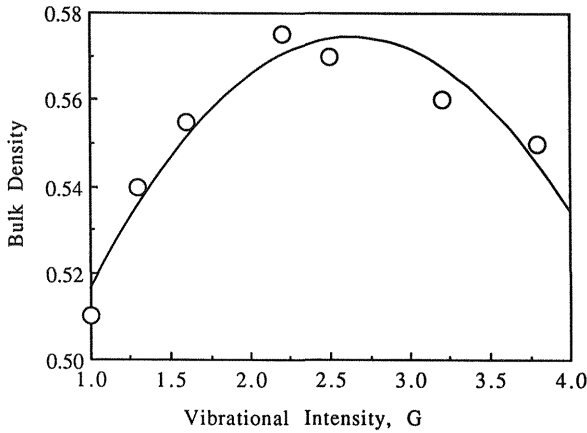


Fig. 16.15 Packing density as a function of vibrational intensity, where $G = a(2\pi f)^2/g$. See text for symbols. (Data from Suzuki et al., 1969.)

SYMBOLS

a = constant in kinetic vibration equation

D = (a) diameter of efflux tube, (b) diameter of cylindrical vessel

d = particle diameter

d/D = reduced diameter

F_r = fraction in rhombohedral arrangement

F_f = fraction of powder bed in cubic arrangement

G = vibrational density

g = (a) twice the width into a bed at which a wall effect is felt; (b) gravitational acceleration

H = height of cylindrical vessel

(h/d) = relative mean spacing in a closely packed bed

k = consolidation rate constant

M = mass of powder

m = mass of grams of fines in a didisperse powder bed

N = average coordination number for a mixture

n = number of taps

S_e = sphericity

V = total volume of a bed

V_1 = volume of a primary sphere

V_2 = volume of a secondary sphere

V_n = volume of sphere in n th order void space_

V_m = unit particle volume

V_s = solids volume of particles in a bed

v_{mix} = volume occupied by a mixture of a fine and coarse component

v_s = solids fraction

x = weight fraction of fines in a didisperse powder bed

- $x_{\max}$ = fraction of fine fraction where maximum density occurs
 $\beta = g/d$ = material-dependent factor connecting diameter of particle and wall effect
 ε = porosity
 Ω = vibrational amplitude
 ρ = particle density
 ε_c = porosity between coarse fraction of a didisperse powder bed
 ρ' = apparent density, bulk density
 ρ_c = particle density of coarse fraction of a didisperse powder bed
 ρ'_f = apparent density of fine fraction of a didisperse powder bed
 $\rho'_{\max}$ = maximum apparent density of a didisperse powder bed
 ρ_{pc} = particle density of coarse component
 ρ_f = particle density of fine fraction
 $\rho'_{\max}$ = apparent density of a mixture of a didisperse powder bed at concentrations of fines above $x_{\max}$
 ρ'_1 = apparent density of a monodisperse powder in an infinitely wide bed
 ρ'_2 = apparent density in layer next to wall of a cylinder, housing a bed of powder
 ρ' = cascaded apparent density
 ρ'_n = apparent density after n taps

REFERENCES

- Arakawa M, Okada T, Suito E (1966). *Zairyo* 15:151.
 BenAim R, LeGoff R (1967). *Powder Technol* 1:281.
 BenAim R, LeGoff R (1968). *Powder Technol* 2:1, 281.
 Berg TWO, McDonald RL, Trainor RJ Jr (1969/70). *Powder Technol* 3:183–188.
 Brown GG (1950). *Unit Operations*. John Wiley & Sons, New York, p 214.
 Carstensen JT (1977). *Pharmaceutics of Solids*. Wiley, New York, pp 63–85.
 Carstensen JT (1980). *Solid Pharmaceutics: Mechanical Properties and Rate Phenomena*. Academic Press, New York, pp 91–95.
 Carstensen JT, Chan PL (1976). *J Pharm Sci* 65:1235–1239.
 Carstensen JT, Puisieux F, Mehta A, Zoglio MA (1978). *Powder Technol* 20:249.
 Crosby EJ (1961). *Kagaku Kogaku* 25:124.
 Furnas CC (1929). *Bur Mines Bull* 307:74.
 Horsfield HT (1934). *J Soc Ind* 53:108.
 Kelly EM (1970/71). *Powder Technol* 4:57–60.
 Kuno H (1958). *Proc Fac Eng Keloh Univ* 11(41):1.
 Leva M, Grummer M (1948). *Ind Eng Chem* 40:415.
 Manegold E, Hofmann R, Solf K (1931). *Kolloid-Z* 56:142.
 McGeary RK (1961). *J Am Cer Soc* 44:513.
 Pitkin C, Carstensen JT (1990). *Drug Dev Ind Pharm*.
 Ridgway K, Rupp R (1969). *J Pharm Pharmacol* 21:30S.
 Ridgway K, Tarbuck KJ (1966). *J Pharm Pharmacol* 18:168S.
 Ridgway K, Tarbuck KJ (1968). *Chem Eng Sci* 23:1147.
 Rocke FA (1970/71). *Powder Technol* 4:180–186.
 Rogers CA (1958). *Proc Lond Math Soc J* 3(8):609–615.
 Roller PS (1930). *Ind Eng Chem* 22:1206–1208.
 Shimohara K (1990). In: Fayed ME, Otten L, eds. *Handbook of Powder Science and Technology*. Reinhold, New York, p 140.

Smith WO (1933). *Physics* 4:425.

Smith WO, Foote PD, Busang PF (1920). *Phys Rev* 34:1271.

Suzuki A, Takahashi H, Tanaka T (1969). *Powder Technol* 2:72.

Wadell H (1932). *J Geol* 4:310.

Wadell H (1934). *J Franklin Inst* 217:549.

White HE, Walton SF (1937). *J Am Ceram Soc* 20:155.:

17

Cohesion

17.1. The Concept of Friction and Frictional Coefficients	299
17.2. The Concept of Cohesion	300
17.3. Repose Angle	302
17.4. Measurement of Cohesion and Friction	303
Symbols	306
References	306

Before progressing in this text, the concepts of cohesion and friction need to be touched on. Friction is of importance in several pharmaceutical aspects. It will be seen in the following chapter, that ease of powder blending is, to some degree, a function of the friction between particles. (This may partly be due to shape factors.) It is also of importance in powder flow and, finally, in the ejection of tablets from tablet dies. The latter aspect necessitates the addition of lubricants (e.g., magnesium stearate) to powder mixes and granulations.

17.1. THE CONCEPT OF FRICTION AND FRICTIONAL COEFFICIENTS

The concept of friction is intuitively obvious, but its definition needs some elaboration.

If an object is placed on a support, then the downward stress would be the gravitational stress (σ , the weight divided by its cross section). To move the object a tangential stress, τ (tangential force divided by the same cross section), is necessary.

There is proportionality between σ and τ ; that is,

$$\tau = \mu\sigma \quad (17.1)$$

where μ is the frictional coefficient. With a setup as shown in Fig. 17.1, the load may be changed, and the tangential force may be graphed as a function of the

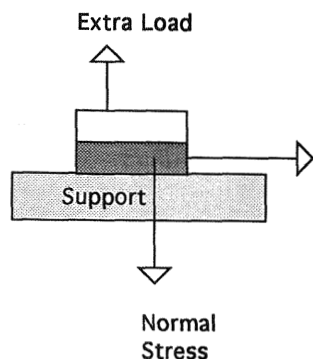


Fig. 17.1 Schematic for the definition of frictional coefficient.

normal load. For a non-cohesive situation this will result in a straight-line where the slope equals the frictional coefficient. Lai and Carstensen (1979), when investigating the frictional coefficient between metal and a tablet surface, compressed a tablet in a die on a hydraulic press, and ejected it part way. The surface of the tablets could then be dragged across a metal plate, and the force necessary to maintain speed could be measured. This could then be repeated with different loads placed on the die.

Although this may have meaning as far as tablet ejection is concerned (e.g., optimum amounts of magnesium stearate can be determined in this fashion), it reveals nothing about the interparticulate friction, which is of such importance in blending and flow.

17.2. THE CONCEPT OF COHESION

Just as frictional coefficients are important in, for instance, blending, so is the concept that to blend particles they must be “pulled away from each other.” This brings in the concept of cohesion, and cohesion and friction are intertwined in many aspects; thus, a discussion of the concept at this point is appropriate.

It is apparent from the foregoing text, that somehow a force must be applied to an object to determine its frictional coefficient with a surface. It is also seen in Fig. 17.1 that the “smallest” load, or normal force, that can be applied is the weight of what “holds” the object in place, in the Lai–Carstensen experiment, the tablet die. Even if this could be made weightless, the gravitational force would always be present, so that zero load cannot be applied as long as the experiment is carried out in a gravitational field such as that of the earth. Hence, one has to extrapolate to obtain zero load.

With powders there are also forces at play that cannot be eliminated, so-called cohesive forces and as will be seen, these must also be estimated by extrapolation.

All particles attract one another. The force q with which two particles attract one another is proportional to their mass m ; that is,

$$q = \beta' d^3 \quad (17.2)$$

where d is the diameter of the particle and β' is a constant. It is also inversely proportional to the square of the distance between them. Assuming d to be the same for both particles, it follows that

$$\beta = \beta''/d^2 \quad (17.3)$$

where β'' is a constant, therefore

$$q = \beta d \quad (17.4)$$

where

$$\beta = \beta' \beta'' \quad (17.5)$$

It has been shown by several investigators (Pilpel, 1964; Bradley, 1936; Hamaker, 1937; Jordan, 1954) that cohesive force is proportional to the diameter of the particle.

The stress σ is the force per unit area, and because the force acts across an area equal to the cross section of the particle it follows that

$$\sigma = b/d \quad (17.6)$$

That is, the cohesive stress is the larger the smaller the particle. This is why fine powders have a tendency to lump, and they will cake-up when stored in drums.

As shown in Fig. 17.2, the individual particle is attracted by all its neighbors. Consider a central particle at A. This particle has a coordination number of N_1 , here, equal to 6, nearest neighbors, and also has interactions with spheres farther away. Each distance, AB or a , is a multiple, γ_i , of d . For example, in the first shell, the distance is simply d . Hence, in general,

$$(AB)_i = a_i = \gamma_i d \quad (17.7)$$

The force between the central sphere and one positioned at B would be

$$q_i = \beta' N_i d^3 / (\gamma_i d)^2 = \beta' N_i d / (\gamma_i^2) \quad (17.8)$$

where N_i is the coordination number of the central particle with particles removed at distances a_i from the central sphere (i.e. the number of particles in the i th shell removed by a_i from the central particle). As stated, there would be several N_i particles in the i -sphere; therefore, the total force exerted on the central particle by all particles is

$$F = \beta' \left(\sum N_i d / (\gamma_i^2) \right) \quad (17.9)$$

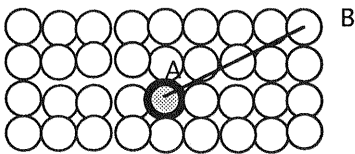


Fig. 17.2 Schematic demonstrating the concept of cohesion in a powder mass. The considerations are made from the central (emphasized) spherical particle and its interaction (e.g., with a particle at position B).

The surface area over which all these forces act is the surface area of the central particle (i.e., $\pi d^2/4$) such that the stress is given by

$$\sigma = \left((4\beta'/\pi) \sum N_i/(\gamma_i)^2 \right) (1/d) \quad (17.10)$$

where the summation is from $i = 1$ to infinity. Obviously, when the distance a_i is more than $3d$, the force contribution per particle will be considerably diminished, but the number of particles will be much greater. It is seen that the stress is inversely proportional to the size of the particle.

17.3. REPOSE ANGLE

An old technique that assesses cohesion and friction is that of the repose angle. Powder is placed in a hopper with the efflux tube blocked. The blocking is released, and the powder flows out and forms a cone on the support below. The flow rate can be monitored in this fashion, and the powder forms an angle α with the support, which is quite reproducible, and is called the repose angle (Fig. 17.3).

A particle on the slant is affected by two forces, the gravitational force, AC and the cohesive force, AB . AC may be broken up by a force parallelogram, as shown in the second inset of Fig. 17.3, and the geometry involved yields a total force perpendicular to the slant plane of $(AB + AD)$. AB is the cohesive force, and AD is the gravitational force times $\cos[\alpha]$ and the tangential force is the gravitational force times $\sin[\alpha]$, so that, putting this in the context of Fig. 17.1, it follows that

$$\mu[C + mg \cos[\alpha]] = mg \sin[\alpha] \quad (17.11)$$

This is one equation with two unknowns, but since both are of importance in pharmaceutical applications, and since the test is very easy to carry out, it still enjoys popularity.

It follows that, assuming spherical particles of diameter d ,

$$mg = g\rho d^3 \pi/6 \quad (17.12)$$

where ρ is the density. Introducing this into Eq. (17.11) gives

$$\mu[C + (g\rho d^3 \pi/6) \cos[\alpha]] = (g\rho d^3 \pi/6) \sin[\alpha] \quad (17.13)$$

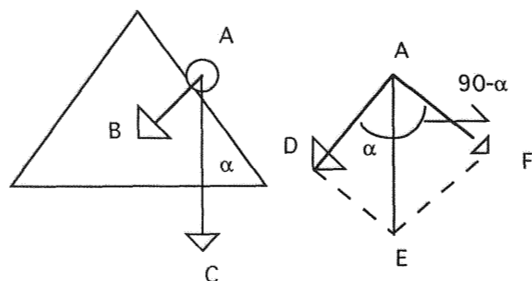


Fig. 17.3 Schematic showing geometry in repose angles.

Carstensen and Chan (1976) have shown the theoretical correlation between the particle size and the repose angle. In general (Pilpel, 1964; Kananiwa et al., 1967; Nelson, 1955; Nogami et al., 1965; Neuman, 1967) have shown that

$$\alpha = (\psi/d) + v \tag{17.14}$$

where ψ and v are constants. Often v is small, so that Eq. (17.14) may be written:

$$\ln[\alpha] = -n \ln[d] + \ln[\psi] \tag{17.15}$$

The result is, however, that n is not necessarily unity (Fig. 17.4).

The limiting value of α as $d \rightarrow \infty$ is v and is often 30° . This is not surprising, because in Fig. 17.5 it is noted that at higher-diameter values the cohesive stress will become small, and at 30° or less, the connecting line between the centers of I and II will form an acute angle with the horizontal (i.e., sphere I will rest in the crevice between spheres II and III, in a configuration that is stable).

17.4. MEASUREMENT OF COHESION AND FRICTION

Cohesion is most often measured by a so-called Jenike shear cell (Jenike, 1961). The principle of this is shown in Fig. 17.6.

The apparatus consists of two cylinders (rings). They are placed, one on top of the other (see Fig. 17.6a). Powder is poured into them, and the powder consolidated (see Fig. 17.6b), to a certain degree, with a plate corresponding to the cross section of the cylinders. From the weight and the volume the porosity and the apparent density of the powder bed can be calculated. A (maximum) load is now applied to the powder (see Fig. 17.6c), and a horizontal force applied to the top ring. The force required to move it (the so-called force at failure, because the integrity of the powder bed fails) is recorded.

The types *Jenike loci* that may result are shown in Fig. 17.7.

If a powder is non-cohesive, then a straight line results, as expected from Eq. (17.1). However, if cohesion occurs, the line will be curved, as shown. The endpoints, D and E , are the load and shear stress components at the degrees of consolidation used. Obviously, in the lower curve ending in E , the consolidation has been less than in the upper curve.

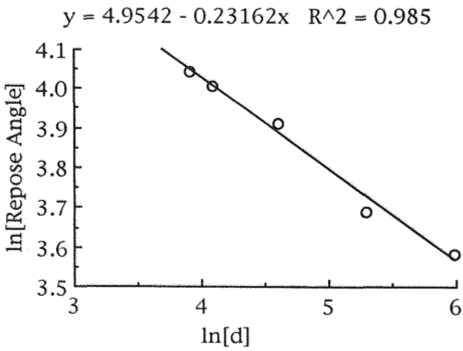


Fig. 17.4 Experimental values of repose angle as a function of particle diameter. (Data from Pilpel, 1964.)

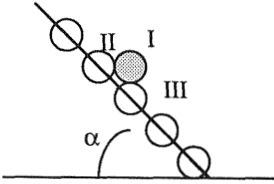


Fig. 17.5 Schematic showing the limiting repose angle of 30° .

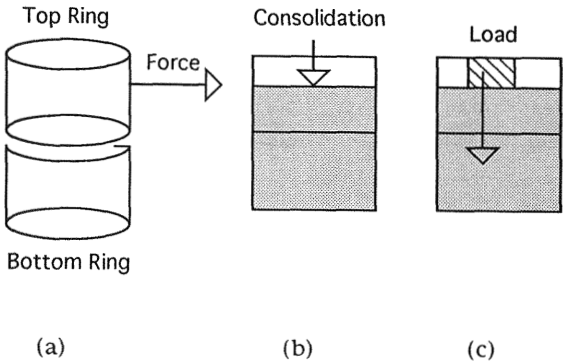


Fig. 17.6 The normal force is the loaded weights plus the weight of the powder and the ring.

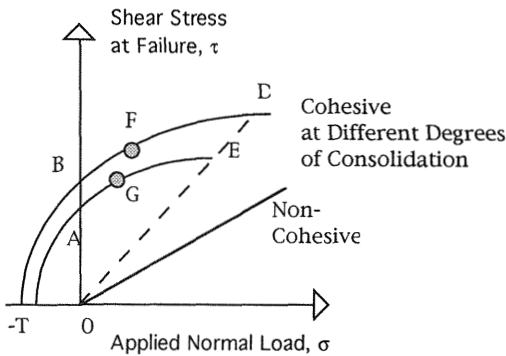


Fig. 17.7 Types of Jenike loci.

Features of the curve are the following: The endpoints to the right (D , E) fall on a straight-line that intersects with the origin, usually at an angle of 45° (Williams and Birks, 1957). The intersect of the curve with the ordinate axis is the stress at zero normal load, and is the value of the cohesive stress C (or force, depending on whether force or stress is used as unit for the axes), for *that powder at that degree of consolidation*. It should be noted that C is a function, therefore, of the state of the powder bed.

The weight of the upper ring and the powder in it constitute the minimum load that can be measured, as represented by the points G and F in Fig. 17.7. Hence, to

obtain C , fairly long extrapolations are necessary. Therefore, it would be advantageous to have another point on the locus. To this end, early researchers assumed that the intersect with the x -axis could be equated with the *tensile stress* of the powder bed.

This may be measured in an apparatus similar to the shear cell, but in place of loads applied to the powder bed, a vertical upward force is applied, and the force at which the powder bed fails is recorded. Hiestand and Peot (1974) have questioned the correctness of this and Carstensen and Geoffroy (1993) have shown, through iterational fits of loci, that this is not true. The curves do follow the Warren–Springs equation but with some slight modification. (Note that Warren–Springs do not infer authors, but rather the location where the method and the equation were developed).

The Warren–Springs equation takes the form, using the nomenclature of Fig. 17.7.

$$(\tau/C)^n = (\sigma + T)/T$$

(17.16)

If the normal load at the endpoints (e.g., D and E) is denoted σ' , then the equation may be expressed as

$$(\tau/\sigma')^n = C^n(\sigma')^{1-n}(\sigma + T)/\sigma'$$

(17.17)

n is the shear index. It frequently follows the relation (Farley and Valentin, 1967; Stanforth and Ashley, 1973)

$$n = 1 + 0.53d^{-2/3}$$

(17.18)

The quoted authors found that

$$C \approx 2T$$

(17.19)

They also found that the tensile strength is related to the maximum stress σ' by the relation

$$T = h(\rho'/\rho)^m$$

(17.20)

where ρ' is the bulk density after compaction, and ρ is the particle density.

An example of the foregoing concepts is represented by the data published by Kocova and Pilpel (1973) as shown in Table 17.1 and Fig. 17.8.

The curves follow the Warren–Springs equation.

Table 17.1 Jenike Locus Data

Tensile strength, T ($N\ m^{-2}$)	Normal stress, σ_N ($N\ m^{-2}$)	Shear at failure τ ($N\ m^{-2}$)
174	330	660
	630	800
	930	940
	1090	1070
226	790	1575
	1090	1920
	1550	2180

Source: Kocova and Pilpel, 1973.

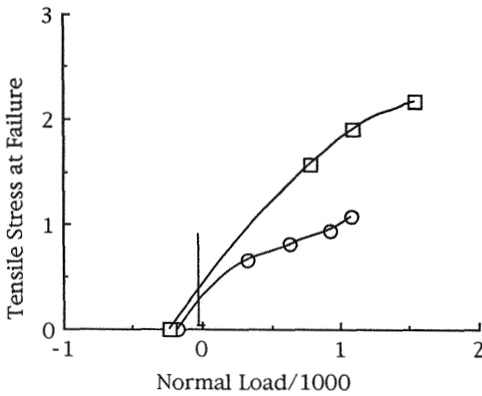


Fig. 17.8 The cohesive stress is indicated by the ordinate axis indicated at $x = 0$. Units are in $Nm^{-2}/1000$. (Data from Kocova and Pipel, 1973.)

SYMBOLS

- a = distance between two spherical particles
- b = constant relating force to diameter
- C = general term for cohesion
- d = diameter of a spherical particle
- g = gravitational acceleration
- h = factor in the correlation between tensile strength and apparent density of bed and particles
- m = (a) mass of a particle; (b) exponent in the correlation between tensile strength and apparent density of bed and particles
- N_i = coordination number spheres of the i th shell
- n = shear index
- q = force with which two particles attract one another
- T = (a) tensile strength of bed; (b) iterant in the Warren–Springs equation
- β, β', β'' = constants relating interparticulate force to diameter of a particle
- α = repose angle
- γ_i = coefficient relating interparticle distance to particle diameter
- μ = frictional coefficient
- ψ = constant in repose angle versus diameter equation
- ν = constant in repose angle versus diameter equation
- ρ = particle density
- ρ' = apparent density of bed
- σ = normal stress
- σ' = maximum normal stress
- τ = tangential stress

REFERENCES

- Bradley RS (1936). Trans Faraday Soc 32:1088.
- Carstensen JT, Chan PL (1976). Powder Technol 15:129.
- Farley R, Valentin FHH (1967). Powder Technol 1:344.

- Geoffroy JM, Cartensen JT (1993). Powder Technol 76:135.
- Hamaker HC (1937). Physica 4:1058.
- Hiestand EN, Peot CB (1974). J Pharm Sci 63:605.
- Jenike AW (1961). Utah Eng Exp Stat Bull 108:1.
- Jordan D (1954). Br J Appl Phys 5:S194.
- Kananiwa N, Ikekawa A, Aoki H (1967). Chem Pharm Bull 15:1441.
- Kocova S, Pilpel N (1973). Powder Technol 8:33.
- Lai T Y-F, Carstensen JT (1979). Int J Pharm 1:33.
- Nelson E (1955). J Am Pharm Assoc Sci Ed 44:435.
- Neuman B (1967). Adv Pharm Sci 2:181.
- Nogami H, Sugiwarara M, Kimura S (1965). Yakuzaigaku 25:260.
- Pilpel N (1964). J Pharm Pharmacol 16:705.
- Stanforth PT, Ashley RC (1973). Powder Technol 7:215.
- Williams JC, Birks A (1957). Powder Technol 1:199.

This Page Intentionally Left Blank

18

Powder Flow

18.1. Powder Flow: Definitions	310
18.2. The Measurement of Repose Angles and Apparent Densities in Flow Experiments	311
18.3. Powder Flow in Tableting	312
18.4. Types of Powder Flow	313
18.5. Correlation Between Particle Diameter and Flow Rate	314
18.6. Correlation Between Repose Angle and Flow Rates	315
18.7. Wall Effects	316
18.8. Effect of Efflux Tube Diameter	318
18.9. Effect of Moisture	319
18.10. Particle Enlargement	319
18.11. Flow of Polydisperse Powders and Powder Mixes	319
18.12. Dynamic Flow Rates	320
Symbols	320
References	321

The prime interest in pharmaceuticals relative to powder flow is that it affects tableting (and hard-shell) operation in several ways.

The flow rate of powders is affected by several properties:

1. The shape of the particle
2. The size of the particle
3. The roughness (rugosity, fractal dimension) of the particle

4. The chemical nature of the powder (e.g., the cohesion)
5. The moisture content

The first sections in the following will deal with the flow of (a) first one fairly monodisperse component, then (b) a polydisperse component or a mixture of two components. If not otherwise specified in the heading, it is example (a) that is being discussed.

18.1. POWDER FLOW: DEFINITIONS

In its simplest form, powder flow is measured by placing powder in an appropriate funnel and blocking off the exit tube. A timer is started at the time point the blocking is released, and the length of time t it takes for the hopper to empty is measured, as is the mass (weight) M of the powder (Fig. 18.1). The flow rate is then:

$$W = M/t(\text{g/s}) \quad (18.1)$$

This type measurement is often performed during the developmental stages of a product and also, during scale-up and manufacturing. It is obvious that this type of measurement also permits measurement of the repose angle.

Although the shortcomings of repose angles has been mentioned, it is a practical parameter, easy to obtain, and helps in the history of a product, or the development of a product. If a series of batches of a drug product are made, and one batch suddenly does not perform in a manner consistent with the others (poor tableting, improper bulk density, or other), then the flow rates and repose angles may also differ, and this may tie in with the problems. Conversely, if it is used as an in-process control, deviation from norm may bode problems in further processing.

There are some instances when it would be more appropriate to express the flow rate in units of cubic centimeters per second (cm^3/s), in which case the flow rate would be:

$$W' = M/(\rho't) \quad (18.2)$$

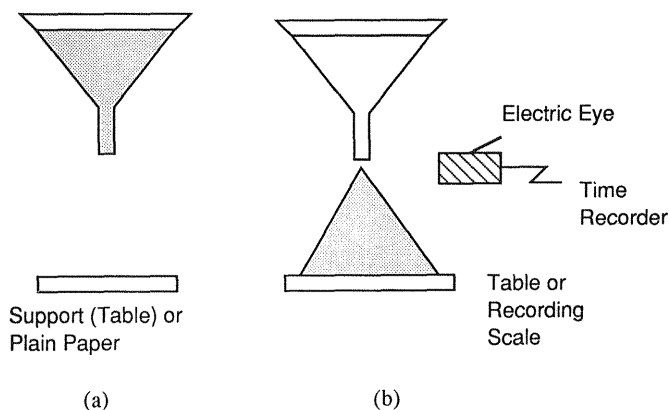


Fig. 18.1 Schematic for static powder flow measurements.

where ρ' is the apparent density of the powder. The problem then is whether it is the apparent density of the powder in the hopper, or that in the conical heap, that is of importance, because they may be different.

Apparatuses have been constructed to facilitate the measurement of the beginning and the end of the flow. The Lewis-Howe flow meter uses a timer, connected with the exit block, an electric beam past the exit of the efflux tube, and when the beam is interrupted the time records as zero, and when it becomes intact again the end time is recorded. This is optional, but refines the measurement.

At times it is not only the flow rate, but the “regularity” of the flow that is of importance. For pharmaceutical operations, flow of powder through the appropriate orifices must be of fairly uniform rate, and poor consistency during the flow operation may be problematic. Consequently, some flow meters are equipped with a recording scale. Hence, the recorded trace will have the shape shown in Fig. 18.2.

In 18.2a the powder is free-flowing. The flow rate is the slope of the line. In Fig. 18.2b the flow is highly irregular. An average flow rate may be estimated (either by least squares or drawing a line by eye—a so-called least-squares wrist), but the important feature is that the flow rate is not uniform, and that problems (e.g., in tableting) may be anticipated.

18.2. THE MEASUREMENT OF REPOSE ANGLES AND APPARENT DENSITIES IN FLOW EXPERIMENTS

Repose angles are often measured in a rather old-fashioned way. The conical heap may be caught on a piece of paper (Fig. 18.1a). The height h of the cone may be measured (best by an optical micrometer i.e., a vertical micrometer with a telescope arrangement). The radius of the cone may be estimated by tracing the (almost circular) contour of the cone on the paper and determining the area A (in the simplest fashion by weighing it and knowing the weight of 1 cm^2). The radius of the cone r is then $\{A/\pi\}^{1/2}$ and the tangent of the repose angle α is

$$\alpha = h/r \quad (18.3)$$

Having the height and the base area, the determination of the volume V is simply, and from this the apparent density ρ'' after flow, may be determined. The determina-

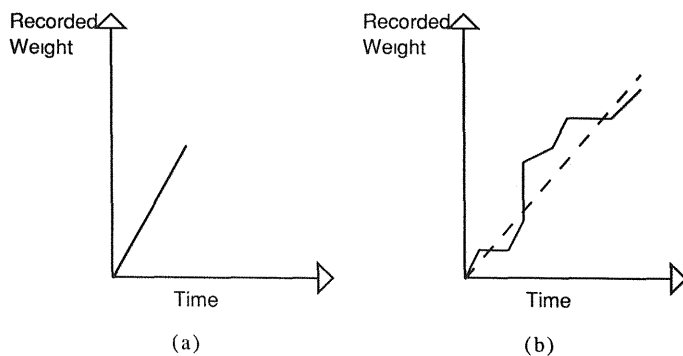


Fig. 18.2 Traces from a recording flow meter.

tion of the apparent density before the flow starts (i.e. in the hopper of the funnel) ρ' may be determined by gradating the funnel. These are two cascaded apparent densities that may (or may not) differ, and may be of value recording, again for the assembly of a data base, should a future batch of powder deviate from the norm.

18.3. POWDER FLOW IN TABLETING

In a tableting operation on a rotary machine, powder is filled into a hopper (Figs. 18.3 and 18.4), this then flows into a feed frame, from whence it flows into the cavities formed by the lower punch and the tablet die. As shown in Fig. 18.3, it is necessary that the powder flow from the hopper into the feed frame, and *also* necessary that the powder flow from the feed frame into the die cavities. This is implied in the figure by having smaller amounts in the die at B1, then more at B2, and even more at B3. With good flow all these may be equal. The description is somewhat simplified, but demonstrates the principles involved.

Hence, there are two aspects of flow in this situation, one is the flow from the hopper into the feed frame, one from the feed frame into the dies.

If the feed frame is a cm long, and the rotational speed of the die table is ω rotations per second (rps), and if the die table has a radius of R , then the linear speed, v cm/s, of a die is

$$v = 2\pi\omega R \quad (18.4)$$

so that the time a die is in contact with the contents of the feed frame τ , is

$$\tau = a/2\pi\omega R \quad (18.5)$$

If the tablet being made has a compression weight of D g, then the flow rate from feed frame into hopper must be at least

$$W = D/\tau = D2\pi\omega R/a \quad (18.6)$$

The value of D is the volume of the die V times the appropriate apparent density ρ' so that

$$W = V\rho'2\pi\omega R/a \quad (18.7)$$

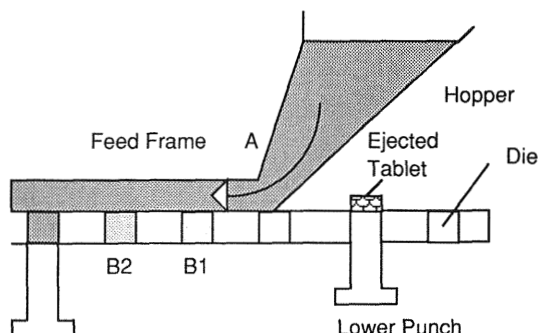


Fig. 18.3 Simplified schematic of powder flow in a tableting operation on a rotary tablet machine. Side view.

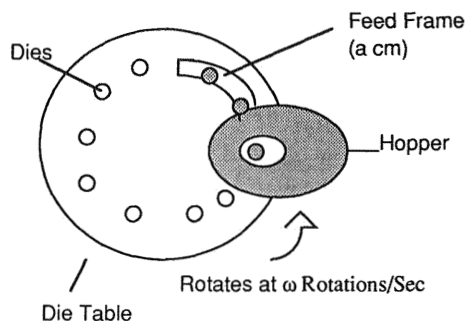


Fig. 18.4 Simplified schematic of rotary tablet operation. Top view.

The weight D' delivered is

$$D' = Wa/2\pi\omega R \quad (18.8)$$

For a given flow rate, Eq. (18.8) denotes the maximum, critical speed, ω_{crit} , at which the desired tablet weight may be obtained. At speeds below ω_{crit} , given by Eq. (18.7), the dies will, therefore, be full at point B3 (provided the flow from the hopper is adequate). At speeds above ω_{crit} the achievable fill weight will drop inversely with the speed, and this is one reason that flow rates are so important. It is economic to operate the machine at as high a speed as possible, and the machine speed is set at such a level, so that the higher the flow rate, the more economic the operation.

Not much recent work has appeared on this subject. Larhrib and Well (1988) have described the effect of the speed of compression on tablets made from polyethylene glycol–dicalcium phosphate mixtures.

18.4. TYPES OF POWDER FLOW

The types of flow that may be encountered is discussed next. Consider the situation shown in Fig. 18.5. Sphere A, (adjacent to the wall of the tube) is affected by gravity (PT), and this force may be dissolved in direction PS (into the wall of the tube) and PQ (toward the sphere B, in the next “row”). Sphere B is affected by the two

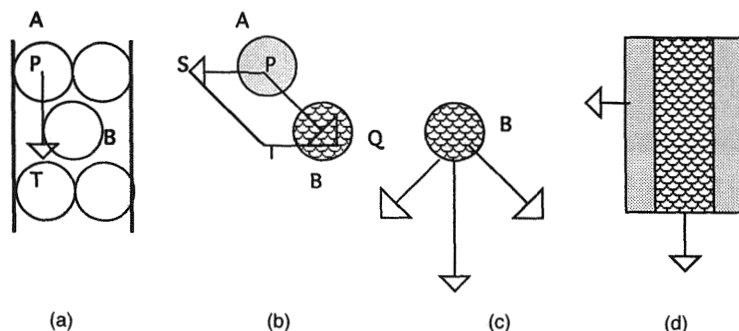


Fig. 18.5 Schematic of flow patterns.

neighbors in the row above it, as shown in Fig. 18.5c, and also by gravity, and all these forces add to a vertical force. The powder mass, therefore, consists of a layer next to the tube, and an interior layer (Fig. 18.5d). The former has a force toward the wall, and the interior a force in the downward direction. If it is the former that governs the flow then the mass moves as a plug (plug flow, akin to laminar flow), and if the interior moves "faster" than the particles close to the wall, then there is particle movement in the cylinder of spheres (turbulent flow), as they move downwards.

For plug flow, the flow rate is larger, the smaller the frictional coefficient is between the particles in the outer layer and the tube, and to the force normal to the tube. The frictional stress is proportional to the contact area between the outer particles and the tube; hence, for a sphere of diameter d , this would be related to πd^2 per particle. If the diameter were halved, then the surface area would be one-fourth, but the number of particles would be eight times as high, so that the contact area would double. Hence, the smaller the particle, the larger the contact area, and the slower the flow.

At very small particle sizes the cohesive stress becomes more important, and at a given particle diameter the cohesive stress in the lowest exposed layer will exceed the gravitational force on the column above it (Fig. 18.6), and there will be no flow.

The flow of poorly flowing powders may be improved by so-called glidants or running-powders, talc for instance (Strickland et al., 1956). Frequently, however, other means of flow improvement must be found.

It is obvious from the foregoing that the two main factors that affect flow are particle shape and size. The closer to spherical the better a particle (powder) flows. Because of the cohesion associated with small particle size, increasing the particle size will improve flow.

18.5. CORRELATION BETWEEN PARTICLE DIAMETER AND FLOW RATE

This is the most important aspect of flow rates. When particles are too fine, they will not flow readily out of a hopper or into a die. There is also an upper limit, because at one point wall effects start being of importance, usually when the particle diameter approaches 1/20 of the efflux diameter. When flow is plotted versus particle diameter, plots such as shown in Fig. 18.7 result (Carstensen and Chan, 1976). Explanation for this are attempted in the following sections.

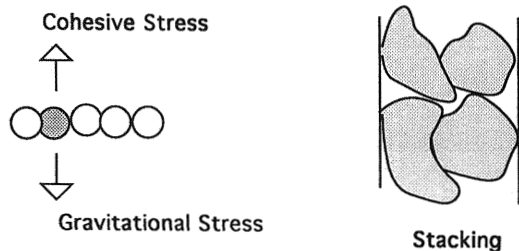


Fig. 18.6 Schematic of blocked flow.

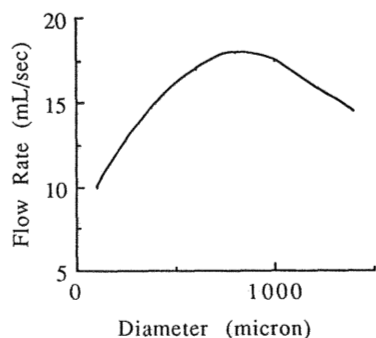


Fig. 18.7 Correlation between particle diameter and flow rate. (Data from Carstensen and Chan, 1977.)

18.6. CORRELATION BETWEEN REPOSE ANGLE AND FLOW RATES

In the past there has been a flurry of publications on this subject (Carr, 1965; Kaneniwa et al., 1967; Fukuzawa et al., 1975; Neuman, 1967; Pilpel, 1971; Gillard et al., 1972).

For the purpose of the discussion to follow, reference is made to Fig. 18.8. In Fig. 18.8a a situation is shown in which the repose angle α , is fairly small, (i.e., $90-\alpha$ is fairly large). If one filled a tube and placed it at an angle of α with the horizontal, flow would not occur (it does not occur on the surface of the conical heap), but if the angle is increased just a bit, particles would flow down from the side of the heap until α is restored. Similarly, a small increase in the angle the tube exerts against the horizontal would cause flow.

Hopper design (the angle of efflux tubes, the slant of the hopper cylinder) is essentially based on affording geometries that work as well as possible for as many types of powder as possible. The flow of the powder is associated with the repose angle, and this as demonstrated in the fashion shown in Fig. 18.8.

The force, necessary for flow is, as seen, just superseded when the angle of the tube is increased beyond the value of α . The larger the contact angle, the less extra force remains to cause flow, so that qualitatively it may be seen that a larger contact angle causes a slower flow rate.

Quantitatively this may be expressed as the "remaining" force, F at vertical position (angle being 90° with the horizontal), being related to the force F_α , at the contact angle (the tangential stress) to have the relation (in line with Fig. 18.8).

$$F = F_\alpha / \cos[90^\circ - \alpha] \quad (18.9)$$

It has been seen in Chap. 17 that the relation between repose angle α and particle diameter d is given by

$$a = (K/d) + Q \quad (18.10)$$

or:

$$d = K/(\alpha - Q) \quad (18.11)$$

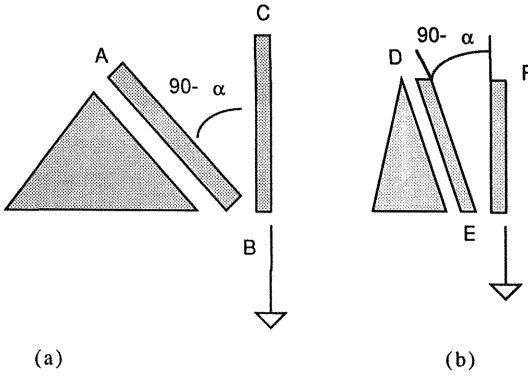


Fig. 18.8 Schematic showing effect of repose angle on flow through a tube.

With knowledge of K and Q , d may be calculated from α by means of Eq. (18.11), and a quantity proportional to flow rate may be calculated as a function of α by way of Eq. (18.9). To test the profile of such relations as Eqs. (18.9)–(18.11) the program in Table 18.1 has been written. The results from the program using a value of $K = 2800$ and $Q = 28.6^\circ$ are plotted in Fig. 18.9.

It accounts for the increase in flow with increasing particle size, but the behavior at high particle diameter is missing.

18.7. WALL EFFECTS

It is seen that the curve in Fig. 18.9 is similar to the one expected at low-diameter values (see Fig. 18.7), except that it does not decrease at very high-diameter values. As demonstrated in Sec. 18.4, it is obvious that if a powder had particle sizes ranging from 100 to 2000 μm , then the larger particles would block an orifice which was 1000 μm wide. This means that there is some upper limit on the fore-

Table 18.1 Data-Generating Profile for Eq. (18.9) to Eq. (18.11), Using a value of $K = 280$ and $Q = 28.6^\circ$

```
PRINT "Angle", "Diameter", "Flow Rate"
FOR X1 = .5236 TO 1.0472 STEP (.15708/4)
REM this represents angles from 30° to 60°
X2 = X1*180/3.1416
Y1 = SIN(x1)
Y2 = 1/Y1
REM This is force, proportional to flow
Y4 = X2-28.6
Y5 = 2800/Y4
REM This is d
PRINT X2, Y5,Y2
NEXT X1
```

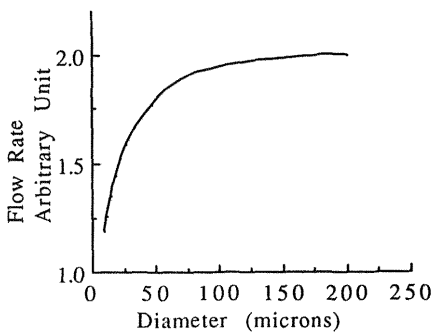


Fig. 18.9 Data generated from the program in Table 18.1 using a value of Q of 28.6° and a value of $K = 280$.

going considerations. Many authors use the reduced diameter d/D , where D is the diameter of the efflux tube, as the workable parameter. In general, when d/D is larger than 0.05 there will be substantial wall effects. For a given tube diameter, $1/D$ will be a constant. This feature may be incorporated in the program in Table 18.1 by adding the steps

$$Y6 = (1/Y2) - U*d \tag{18.12}$$

where U is a constant, characteristic of the powder. This has been done in the program in Table 18.2. The printout using the values $K = 2800$, $Q = 28.6$, and $U = 0.0002$ results in the data in Table 18.3 and the data are plotted in Fig. 18.10.

Table 18.2 Program in Which Wall Effects Are Taken into Account [Eq. (18.12)]

```
INPUT "K-value="; K
INPUT "Q-value="; Q
INPUT "U-value="; U
PRINT "Angle", "Diameter", "Flow Rate"
FOR X1 = .5236 TO 1.0472 STEP (.15708/4)
  REM this represents angles from 30° to 60°
  X2 = X1*180/3.1416
  Y1 = SIN(x1)
  Y2 = 1/Y1
  REM This is force, proportional to flow
  Y4 = X2-Q
  Y5 = K/Y4
  REM This is diameter
  Y6 = Y2 - (U*Y5)
  REM this is adjusted flow rate
  REM Y5 is d
  PRINT X2, Y5,Y6
NEXT X1
```

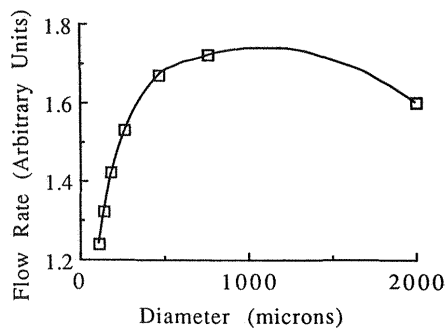


Fig. 18.10 Data from Table 18.4.

By comparing this curve with Fig. 18.7 it is seen that it has the expected shape throughout the diameter range.

18.8. EFFECT OF EFFLUX TUBE DIAMETER

It stands to reason that the larger the diameter of the efflux tube, the more rapid the flow. The equation by Brown and Richards (1960) is of the following form:

$$4W/(\pi\rho_pg)^{0.4} = \gamma D + \beta \tag{18.13}$$

where D is the orifice of the efflux tube and β is a constant that depends on the particle diameter, d . It is noted that this translates into a dependence on orifice diameter of $D^{2.5}$ (i.e., a power of 2.5). This has been verified by Danish and Parrott (1971), and a similar dependence was found by Jones and Pilpel (1966a,b, and c) who arrived at the following equation:

$$W = (A^{-2.5}15\pi)W\rho_pg^{1/2}D^{2.5} \tag{18.14}$$

where ρ_p is particle diameter.

Table 18.3 Printout from Program in Table 18.3 Using the Values $K = 2800$, $Q = 28.6$, and $U = 0.0002$

Repose angle, α	Diameter, $d(\mu\text{m})$	Flow rate, arbitrary units
30	2000	1.6
32.25	767	1.72
24.5	474	1.67
39	269	1.53
43.5	188	1.42
48	144	1.32
52.5	117	1.24

18.9. EFFECT OF MOISTURE

Neuman (1967) found that moisture in solid samples acts as an enhancer of flow, is a “running powder” or a glidant, when present in small amounts, but with larger amounts slows down flow. The effect of moisture makes many flow experiments somewhat uncertain. At one time I was called in as a consultant on a flow situation, where the flow blocked in a tableting operation. When the demonstration of this took place, the powder ran fine, and tableting was no problem. It was simply a matter of relative humidity in the room. In very few investigations has the relative humidity in the environment been subject to scrutiny. This is a factor that should be included in such experiments, and should be considered in assessment of published data.

18.10. PARTICLE ENLARGEMENT

There are many reasons for keeping drug particles small. For instance, dissolution is improved with the larger specific surface area associated with the smaller particle, content uniformity, as will be seen in a later chapter, is improved with smaller particles.

But from the point of view of flow, it is obvious that (below the maxima) particle enlargement is of importance. Particle size enlargement, therefore, is often a necessity, and it will be the subject of several subsequent chapters, but for completion, it is mentioned here that it can be accomplished in four ways: slugging, roller compaction, wet granulation, and spray-drying.

In addition to this, manipulation of the drug recrystallization (rate of cooling, for instance), may give some control over the particle size distribution and, thereby, the flow rates of a powder.

18.11. FLOW OF POLYDISPERSE POWDERS AND POWDER MIXES

Powder mixes are mostly polydisperse, so the two situations may be treated as one. First, technologists often talk about “fines” in a powder. In general pharmaceutical operations are geared at producing polydisperse powders of a fairly narrow particle range (e.g., granulations). The presence of material that is much finer, weight percentage-wise, than the particle size of the largest fraction is often deleterious. In tablet operations, for instance, it is associated with (although not necessarily the mechanical reason for) a defect known as a “capper” (i.e., a tablet where the crown has the potential of dislodging itself).

However, in small amounts the fines may act as a glidant (Danish and Parrott, 1970 Strickland, 1956). They, in small amounts, tend to stick to surfaces of larger particles and “keep them apart.”

For powders that have a certain percentage of an ingredient or fraction (on a number percent basis) that is much coarser than the remainder, the problem of segregation occurs. This will be treated in some detail in chapters to follow, but suffice it say, here, that if a repose angle experiment is carried out, the coarse particles will “roll down” and separate out at the base of the conical heap. The same type of behavior will occur when a powder is discharged from a mixer into a drum, so that in such situations the initial transfer will result in a larger proportion

of coarse particles at the wall of the drum into which the powder was discharged, than in the center. If the coarse fraction is an active component (e.g., vitamin A beadlets), then this may be a source of content uniformity problems.

With polydisperse powders where no size “predominates” (e.g., of maximum density as described in Chap. 16), repose angles are fairly reproducible and the conical heaps are fairly uniform.

18.12. DYNAMIC FLOW RATES

It is tempting to try to simply calculate the adequacy of a powder blend for a tableting operation by obtaining the flow rate by one of the mentioned methods, and then calculate (a) how much will flow out of the hopper per time unit, and (b) how much will flow into the tablet die. The diameters of the orifice of the hopper is known, as is the diameter of the die, and because the test is nondestructive, it is possible to actually perform the flow rate experiment using the hopper and, similarly, to have a flow meter using a die as the efflux tube.

For the hopper, there is sufficient vibration in a tableting operation to make the statically found flow rate wrong and, furthermore, the level of powder will change. It should be noted that this latter is not all that important, but the vibration is. In general the vibration *helps*. For cohesive powders, there are machine attachments (forced feeders) at the bottom of a hopper, that will help the flow along, and these are used very often, particularly in direct compression.

For the flow into the die, there is a profound difference. Carstensen and Laughlin (1979) constructed an experimental apparatus in which a rectangular die table (with one die) could be moved below a hopper with a rectangular opening of length a on the bottom. A bin below the die table would then catch the powder that flowed through the die. In this instance, the mass (weight) M of powder could be determined for an experimentally determined time, t . The velocity would then be: $v = a/t$, and the flow rate W would be M/t . They found the flow rate to be a function of die table velocity by:

$$\ln[q - W] = \ln[v] + \ln[k] \quad (18.15)$$

where q and k are constants. The apparent density of the material flowing through the die is less than even the cascaded apparent density, so that compression of powders on high-speed machines occurs where the material has a lower density than the densities that may be determined by more static means in the laboratory.

SYMBOLS

A = (a) area of the base of a cone in repose angle determination; (b) constant in the Jones–Pilpel equation

a = (a) length of a feed frame; (b) length of die table in Carstensen–Laughlin experiment

D = (a) grams of powder in a die; (b) diameter of orifice of efflux tube

D' = D = grams of powder in a die

F = force acting on powder in a tube

F_α = force just sufficient to *not* allow a particle to slide down the slant of a cone

h = height of a cone in repose angle determination

K = constant in the equation relating repose angle to particle diameter
 k = constant in the Carstensen–Laughlin equation
 M = mass of material flowed into or through a die
 Q = constant in the equation relating repose angle to particle diameter
 q = constant in the Carstensen–Laughlin equation
 R = radius of die table
 r = radius of a cone in repose angle determination
 rps = rotations per second
 t = time
 V = (a) volume of cone in repose angle determination; (b) volume of a die
 v = linear speed of a die
 W = flow rate (g/s)
 W' = volumetric flow rate
 α = repose angle
 β = constant in the Brown and Richards equation
 γ = constant in the Brown and Richards equation
 ω = rotational speed
 ρ' = apparent density of material in a hopper
 ρ'' = apparent density after flow
 ρ_p = particle diameter
 τ = contact time between powder and die

REFERENCES

- Carr R (1965). *Chem Eng Lond* 72(C):163.
 Carstensen JT (1981). *Solid Pharmaceutics, Mechanical Properties and Rate processes*. Academic Press, New York, pp 96–99, 184.
 Carstensen JT, Chan PL (1977). *J Pharm Sci* 66:1235.
 Carstensen JT, Laughlin S (1979). *Powder Technol* 23:79.
 Danish FQ, Parrott EL (1971). *J Pharm Sci* 60:550.
 Gillard J, L, Jaminet F, Roland M (1972). *J Pharm Belg* 27:713.
 Fukuzawa H, Fukoka E, Kimura S (1975). *Yakugaku Zashi* 95:859.
 Jones T, Pilpel N (1966a). *J Pharm Pharmacol* 18:31.
 Jones T, Pilpel N (1966b). *J Pharm Pharmacol* 18:182S.
 Jones T, Pilpel N (1966c). *J Pharm Pharmacol* 18:429.
 Kaneniwa N, Ikekawa A, Aoki H (1967). *Chem Pharm Bull* 15: 1441.
 Lahrib H, Wells JI (1998). *Int J Pharm* 160:197.
 Neuman B (1967). *Adv Pharm Sci* 2:181.
 Pilpel N (1971). *Adv Pharm Sci* 3:174.
 Strickland WA Jr, Busse L, Higuchi T (1956). *J Am Pharm Assoc Sci, Ed* 45:482.

This Page Intentionally Left Blank

19

Comminution

19.1. Physics of Grinding	323
19.2. Ball Mills	324
19.3. Hammer Mills	327
19.4. Fluid Energy Mills (Attrition Mills, Micronizers)	330
19.5. Milling-Induced Particle Size Distributions	330
19.6. Milling-Induced Changes in Morphology	332
Symbols	333
References	334
Recommended Reading	334

The word *comminuting* denotes particle size reduction, however, the word *milling* is most often used. The former word simply denotes that particles have been made smaller, the latter word implies the manner in which it is done. The words may be used interchangeably.

As mentioned in the introduction, this book does not cover individual pieces of equipment. The introductory remarks to this chapter are simply that the intent is to outline the principles by which milling equipment works.

19.1. PHYSICS OF GRINDING

The principle of grinding is that all particles have flaws, and that impact will cause crack propagation. In general, a crystalline solid, when exposed to stress will first deform elastically (i.e., it will in this region, return to its original shape when the stress is removed). Hooke's law

$$\text{Strain} = \beta_1 \text{stress} \quad (19.1)$$

applies in this region. In this region, if the stress is released, then the particle will return to its original shape. If the stress has not been applied for too long of a time, the density will also remain unaltered. For stress, applied for long time periods, there could be some vacancy release, and the density could increase ever so slightly

Beyond a certain point (Fig. 19.1), the yield point, the elastic limit is exceeded, and the solid will deform. This is denoted *plastic deformation*. It is obvious that in this region the crystal lattice is strained, and in certain types of milling (ball milling of long duration), amorphicity may result. In regions beyond the plastic limit, the particle will not, if the stress is released, return to its original shape.

At a given point, the fracture point, the crystal “breaks.” These concepts are important in milling, but even more important in compression.

19.2. BALL MILLS

It has been seen in previous chapters, that surface area and particle size distribution are of importance in pharmaceuticals. Usually, raw materials, as received or synthesized, do not have the “correct” particle size and surface area. To attain this they are milled, and milling is the first unit operation that is encountered in pharmaceutical production and development.

At the preformulation stage of product development, mortar and pestle are the means of grinding. At this stage only small amounts of drug substance are at hand, necessitating small equipment that can be operated with a minimum of powder loss. The findings using preliminary procedures are often nonapplicable to the findings later on in the development of a drug, when larger-scale means are used.

Types of mills that will be discussed here are ball mills, hammer mills, and fluid energy mills (micronizers). Ball mills are usually used only in early stages, and the work horses in scale-up—even moderate scale-up—are the hammer mills.

The principle of a ball mill is shown in Fig. 19.2. Powder and balls are charged into the cylinder (in upright position), a lid is placed on the open end and secured, the cylinder is then laid horizontally on a pair of rollers, which roll at a predetermined speed.

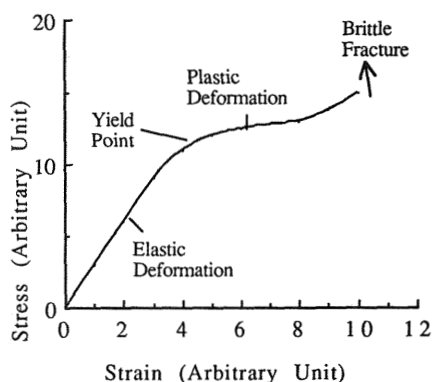


Fig. 19.1 Stress-strain diagram for a solid.

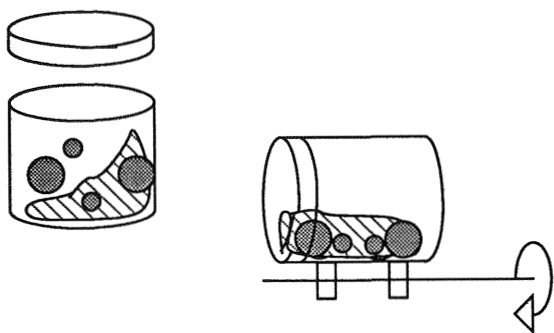


Fig. 19.2 Principle of ball mill.

The degree of comminution depends on (a) the size of the balls, (b) the ratio of balls to powder, and (c) the speed of the mill. There is an optimum amount (weight) of balls to powder, but in general, the mill is supplied with the optimum amount of balls, and the maximum and minimum amount of powder is recommended for a particular mill. In general, there are eight balls of a radius of one-fifth to one-tenth of the radius of the cylinder, r . In general, the mill should be only one-third full.

The mill may be operated at different speeds. At lower speeds, the intensity of milling increases with speed, but there is an upper limit, and when the centrifugal limit is reached, the balls will simply sit toward the wall of the mill and not move within the mill, and then no comminuting takes place. This is the centrifugally limiting speed, which is (in radians, ω).

$$\omega = (g/r)^{1/2} \quad (19.2)$$

Ancient milling was carried out with millstones, and in smaller scale this is used in *mortars and pestles* in the laboratory. In liquid processing, the homogenizers that depend on rotating cones and stators are based on this principle.

Ball mills are frequently used in laboratories, but rarely in pharmaceutical production.

Not too much attention will be paid to the foregoing two types of mill in this text, because they are only of very small-scale interest. However, the morphological changes that may occur in a powder through milling are very possible in both mortar-and-pestling and ball-milling.

Ball mills have also been of interest in studies of milling kinetics. Comminution is generally considered a first-order process (Austin et al., 1977; Gardner and Robers, 1975; Gardner and Austin, 1975; Austin, 1971/1972; Reid, 1965; Jindal and Austin, 1976). Austin (1971/1972) found that milling will cause the mass of material that is of the original size, to decrease in time t . If w grams are milled, then the mass w_a , of material with the original diameter d' , at time t , will decrease by

$$\ln[w_a/w] = -kt \quad (19.3)$$

There are, however, examples where this does not hold (Austin et al., 1976).

Carstensen et al. (1978) and Mehta et al. (1977) have shown the following treatment to hold for pharmaceutical powders and granulations. If a milling is

carried out such that the milled material has a mean diameter of d'' , and the original powder one of d_a , then Kick's law (Parrott, 1970) is expressed as follows:

$$E = C \ln[d_a/d''] \quad (19.4)$$

where E is energy input and C is a constant depending on milling equipment and substance. At a given time t , there will be a certain amount w_b , of the material that will have reduced in particle size to d_b , and a certain amount w_a , that is still of the original diameter $d_a (= d'')$.

The weight mean diameter of the particles then is d'' given by:

$$d'' = (w_a d_a + w_b d_b) / w \quad (19.5)$$

where

$$w = w_a + w_b \quad (19.6)$$

It follows that

$$\ln[d'/d''] = \ln(w d_a / \{(w_a d_a + w_b d_b)\}) = -\ln[(w_a/w) + (w_b d_b / w d_a)] \quad (19.7)$$

Kick's law differs somewhat from Rittinger's law, which states that if the energy is used to create surface ΔA , then, assuming a surface energy of β_2 erg/cm², the energy input will be

$$E = \beta_2 \Delta A \quad (19.8)$$

It has been discussed in earlier chapters that

$$\text{Area/volume} = \Gamma/d \quad (19.9)$$

where

$$\Gamma = \alpha_s / \alpha_v \quad (19.10)$$

where α_s and α_v are surface and volume shape factors. Introducing this into Eq. (19.8) gives

$$E = Q\{(1/d_2) - (1/d_1)\} \quad (19.11)$$

Bond has suggested that it is square root-dependent; that is,

$$E = Q\{(1/d_2)^{1/2} - (1/d_1)^{1/2}\} \quad (19.12)$$

It is obvious, in any event, that energy increases with increased surface.

The energy input is proportional to time; that is,

$$E = q_1 t \quad (19.13)$$

where q_1 is a constant, depending on mill and equipment. Employing Kick's law in the following and combining Eqs. (19.4) and (19.13) then gives

$$E = C \ln[d'/d''] = -C \ln[(w_a/w) + (w_b d_b / w d_a)] = q_1 t \quad (19.14)$$

or

$$y = \ln[(w_a/w) + (w_b d_b / w d_a)] = -Kt \quad (19.8)$$

where

$$K = q_1 / C \quad (19.15)$$

Carstensen et al. (1978) showed that values of d_b , determined experimentally, correlate with iterated values that impart linearity to the experimental data.

19.3. HAMMER MILLS

From a practical point of view, the *hammer mills* (Fig. 19.3) are the most common.

Powder enters the feeding hopper, from which it enters the mill house, where hammers rotate. The powder will have a certain residence time in the mill house, and particles will fracture under the impact of the hammers and, when sufficiently small, will exit through the screen on the bottom of the mill house.

Because of the whirl caused by the rotating hammer, the particles will not leave the mill house perpendicularly, but rather at an angle, so that the particles are always smaller than the opening in the screen. This effect is more pronounced the higher the speed of the hammers.

There are usually three speed settings. The hammer is wedged on one side and if this side is forward in the rotation it is denoted “sharp-edge forward.” The other side of the hammer is simply straight, and if it is forward in the rotation, then one refers to it as “blunt edge forward.” This latter has a greater commuting effect than the former. The higher the speed, the smaller the particle.

The energy of the milling can be changed in several aspects: (a) the speed of the hammers may be changed, or (b) the direction of the hammers may be changed (blunt end or knife end forward). There is a relation between the size of the screen opening and the feeding rate. The former will be a function of the degree of reduction of the original particles. If they are large relative to the screen opening size, then their residence time in the mill house must be longer; hence, the feed rate must be smaller.

Screens in the most common mills (where the energetics are intermediate at best) are interchangeable. They may be either metal wire on a metal frame, or for the larger sizes, they may be metal screens with holes in them. It should be noted (Fig. 19.4) that the particles that have left the mill house are always smaller than the screen

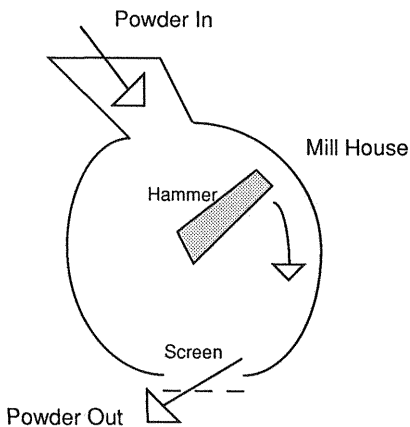


Fig. 19.3 Hammer mill principle.

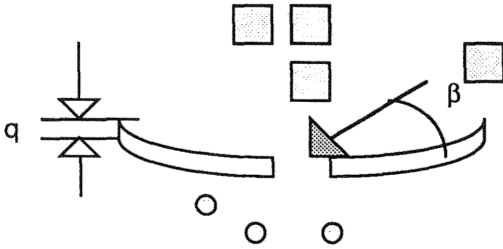


Fig. 19.4 Manner in which a particle exists, the direction being at an angle to the direction of the opening.

opening q . For one thing, the direction of exit is at an angle with the screen (e.g., an angle β); hence, the effective exit area for a particle is $q \cos[90 - \beta] = q \sin[\beta]$.

An example of the correlation between screen opening size, and the produced average particle size is shown in Fig. 19.5.

Heat is evolved during the milling process, and many mills are jacketed, so that they may be cooled. When particles are milled to the 15 to 50- μm range, then the milling step is often referred to as micropulverizing. This is done in jacketed mills and (depending on the cooling liquid) is often referred to as *cryogenic milling*. In some operations it is a practice to add dry ice directly to the feed, but this may cause metal fatigue and cause breakage of hammers (which may then project through the mill house). If done in this fashion, the air must be very dry, otherwise, considerable condensation (i.e., moisture increase) may result.

Many mills are equipped with controlled-feeding devices. This is because, if a powder is fed too rapidly, then the mill cannot handle the load, and the mill house will fill up. The optimum rate is the maximum rate that will permit milling without blockage of the mill house.

Relative to the optimum *rate of milling*, one view is to consider that if N_0 particles are introduced into the mill house per minute, then, at the optimum milling rate, N will survive fracture in an exponential manner; that is,

$$N = N_0 e^{-kt} \tag{19.16}$$

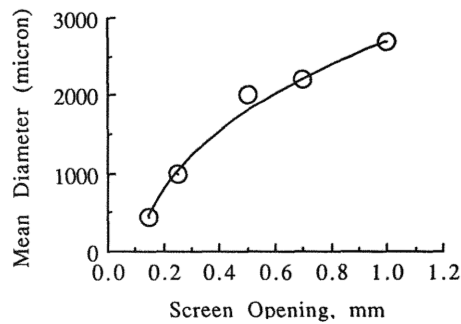


Fig. 19.5. The mean particle size of a milled powder as a function of the screen opening size. (Data from Carstensen, 1993.)

If the particles are not too different in size, then the mass M will be proportional to N , so that

$$M = M_0 e^{-kt} \quad (19.17)$$

If the mill is operated at a higher input, then material will accumulate in the mill house. The efficiency of the milling operation would be given by the ratio M/M_0 so that at optimum efficiency, the residence time τ is

$$\tau = [\ln(M_0/M)]/k \quad (19.18)$$

If (95% of) the incoming powder is (above) a certain size D_0 , then determining the amount that passes through a screen of this aperture after milling for t minutes, gives a value of M_0/M . This can then be carried out over several time periods, and k can be determined from the plot; τ is then determined when it is determined what M/M_0 value is satisfactory.

This point of view often suffices, but throws no light on the particle size distribution that may be expected from a hammer mill operation.

Steiner et al. (1974) studied the effect of milling on the distribution of particle sizes in the milled material. When granules are soft, then the distributions will tend toward normal distributions, but hard granules seem to mill into lognormally distributed stock. In between the particles will be either bimodal or will follow a Weibull function:

$$\ln(-\ln[f]) = \beta_3 \ln[x/\phi] \quad (19.19)$$

where f is cumulative fraction above a diameter of x , and β and ϕ are Weibull parameters.

The bimodal distributions often occur when granules are produced by insufficient granulation (i.e., in the process a part of the material has been granulated, but part is still left the way it was before the addition of the granulating liquid).

As mentioned, energy input is related to the increase, ΔA in surface area A [see Eq. 19.8] where β is the surface energy. In a holed plate screen, each hole will cause a resistance, which in turn gives rise to the energy E , expended, and this is assumed proportional to a $d^{-\lambda}$ where the constant, λ , is a function of hole size, equipment, and the material itself. E is also inversely proportional to the area through which the milled powder is forced. The larger the area, the less the resistance (i.e., the larger the number of holes n , the smaller the resistance), so that the following equation would describe the energy consumption:

$$E = \alpha_2 [d^{-\lambda}/n] \quad (19.20)$$

Equating Eqs. (19.8) and (19.20) gives:

$$-\lambda \ln[d] + \ln\{\alpha_2/\beta_2\} = \ln(n\Delta A) \quad (19.21)$$

Steiner et al. (1974) found Eq. (19.21) to hold well for nine pharmaceutical granulations.

At times, cooling is necessary in milling. Steendam and Lark (1968) report the use of cryogenic milling to grind granules of poly(DA-lactic acid) of high molecular weight ($MW = 85 \times 10^3$).

Adolfson et al. (1998) have shown that milling of sodium chloride (a) makes it more difficult for particle surfaces to rearrange (and, hence, makes solid bridging in tablet formation more difficult), (b) increases the deformability of asperities in the surface, and (c) affects fracture propagation in tablets.

19.4. FLUID ENERGY MILLS (ATTRITION MILLS, MICRONIZERS)

If really large surface areas are required, other means than plain hammer mills must be sought. (The most powerful hammer mills (micropulverizers) have very massive hammers, strong screens, and are jacketed for cooling. Even so, the minimum particle size attainable with them is 20–50 μm .)

These are attrition mills. Air is introduced in two positions of a flat cylinder. The air at the two inlets is introduced at different pressures, so that a strong turbulence is created in the milling chamber. This causes particles to hit one another and break one another. The fine powder is removed centrifugally and is caught in cyclones and airbags. There is always danger of dust explosions under such circumstances, and micronizers are usually housed in separate explosion-proof rooms.

The particle sizes attained are 1–20 μm . The specific surface areas (for pharmacokinetic purposes) are minimally about 3–4 m^2/g . The original material is usually premilled so that it has a particle size of 20/100 mesh.

19.5. MILLING INDUCED PARTICLE SIZE DISTRIBUTIONS

For *granulations* (to be covered in Chap. 21), the particle sizes are usually large, and the usual means of obtaining particle size distributions is by way of *sieve analysis*. By this method, sieves are stacked on top of one another (a nest), the coarsest screen on the top. Usually 100 g of granulation is placed on the top sieve, and the nest is then shaken in a prescribed and reproducible fashion. After shaking, the sieves are separated, and the amount of material on each sieved determined by weighing.

The types of distribution curves obtained are, depending on the granulation process and the milling conditions, normal, lognormal, Weibull, or bimodal (Steiner et al., 1974). What is of practical importance is the percentage of *fines* (particles smaller than 200 μm), for too large a percentage of fines will cause problems when the granules are tableted. The number of fines are a function of (a) the adequacy of the granulation procedure, and (b) the time and intensity of milling. In the former, a certain number of “original” particles never become agglomerated, and reappear in their native state in the final granulation. Because of their lack of binder, they do not contribute to the bonding in the tablet, and too large percentages may cause tablets to split (cap) along failure lines made up of adjacent fine particles or pockets of fine particles.

In the second, it is a case of small, *granulated* particles, and as such, there is not too much harm done in having a certain *small* percentage of fines. As mentioned, the

effect of milling time may be expressed as the percentage P of material retained on a sieve size d' , where d' is a function of milling time t . Carstensen et al. (1978) and Mehta et al. (1977), have shown, that this relation is approximately semilogarithmic.

$$\ln[P] = -kt \tag{19.22}$$

Carstensen and Patel (1974) have shown, on a probability basis, that if a monodisperse powder is fed at a constant rate into a hammer mill, then the resulting ground powder will be lognormal by number.

Assume that there are N particles of initial size x_0 in a sample to be milled. It is assumed that each impact (of the hammers in the mill) will fracture a given fraction α , of the population, and for simplicity it is assumed that each impact will break a particle in half.

Therefore, *after one rotation*, $N(1 - \alpha)$ of the particles will be left unchanged and $2\alpha N$ of the particles will have a size of $x_0/2$. The total number of particles is now $N(1 + \alpha)$.

After two rotations a similar argument will show that a fraction $(1 - \alpha)$ of the $N(1 - \alpha)$ particles of original size [i.e., $N(1 - \alpha)^2$ will remain unchanged], that a fraction of $(1 - \alpha)$ of the $2N\alpha$ particles [i.e., $2N\alpha(1 - \alpha)$ particles] will remain of size $x_0/2$, and that a fraction α of the $2N\alpha$ particles with size $x_0/2$ will be halved (i.e., that there will be $2N\alpha^2$ particles of size $x_0/4$). The total number of particles is now $N(1 + \alpha)^2$.

Proceeding in this fashion, the data in Table 19.1 are obtained.

The number of particles after m impacts is $N(1 + \alpha)^m$ and the possible sizes are from $(x_0/2^p)$ to x_0 . Here, p is a number between 0 and m , and as seen in the table, the fraction that has a size of $x = x_0/2^p$ is

$$N^{(m)}_p(2\alpha)^p(1 - \alpha)^{m-p} \tag{19.23}$$

The fraction of size $x_0/2^p$ is therefore

$$Pr(x_0/2^p) = (1 + \alpha)^{-m} N^{(m)}_p(2\alpha)^p(1 - \alpha)^{m-p} \tag{19.24}$$

The distribution on the right-hand side is normalized binomial, and for large m -values this will approach a normal distribution. The particle diameters are loglinear, because (e.g., $\ln[2^{n+1}] = \ln[2] + \ln[2^n]$), regardless of what the value

Table 19.1 Number of Particles that Remain After N Impacts

Size	Impacts			
	1	2	3	m^a
x_0	$N(1 - \alpha)$	$N(1 - \alpha)^2$	$N(1 - \alpha)^3$	$N(1 - \alpha)^m$
$x_0/2$	$N2\alpha$	$4N\alpha(1 - \alpha)$	$4N\alpha(1 - \alpha)^2$	$Q_1 2\alpha(1 - \alpha)^{m-1}$
$x_0/4$		$4N\alpha^2$	$6N\alpha^2(1 - \alpha)$	$Q_2 4\alpha^2(1 - \alpha)^{m-2}$
$x_0/8$			$N2\alpha^3$	etc.
Total	$N(1 + \alpha)$	$N(1 + \alpha)^2$	$N(1 + \alpha)^3$	$N(1 + \alpha)^m$

^aThe number Q_i implies combinatorial m over i [i.e., (m_i)].

of n is. Hence, for large m values the distribution, therefore, will approach lognormality.

Zhang and Johnson (1997) have used a Bantam mill (Bantam Micro-Pulverizer, Pulverizing Machinery, Summit, NJ) equipped with a herringbone screen at 0.02 in., and using a 14,000 rpm hammer speed and a Jet mill (Jet-O-Mizer, Fluid Energy Alljet, Plumsteadville, PA) at a 90 psi pressure and nitrogen gas to mill an experimental drug (CP 118 954). They found the particle distributions by weight to be lognormal with means of 6 and 18 μm .

19.6. MILLING-INDUCED CHANGES IN MORPHOLOGY

Recent literature abounds with reports of milling increasing surface energy and causing distortion of crystal lattices (in addition to the comminution) (Yamaguchi and Sakamoto, 1959). It is also a common practice to cogrind drugs with polymers, such as HPMC (Sugimoto et al., 1998), β -cyclodextrin (Mitrevic et al., 1996; Arias et al., 1997), chitin and chitosan (Koh et al., 1986a,b), microcrystalline cellulose (Yamamoto et al., 1974, 1976; Nakai et al., 1978), and gelatin (Kigasawa et al., 1981). This increase in surface energy is presumably and primarily due to conversion of crystalline to amorphous solid, and manifests itself in an increase in dissolution rate. Shin et al. (1998) studied cogrinds of furosemide with crosspovidone (polyplasdone, PVP), and found an increase in dissolution rate. The increase in dissolution rate is not due to the presence of cross-povidone, because simply grinding gives the same result as cogrinding.

Briggner et al. (1994) employed isothermal microcalorimetry in the study of changes in crystallinity induced during the milling of powders (Fig. 19.6).

Figure 19.6 shows the effect of applied pressure in a fluid energy mill on the amount of amorphous material produced. The least-squares fit is $y = -0.83 + 2.16x$, with a correlation coefficient of $R = 0.99$. The intercept is not significantly different from zero.

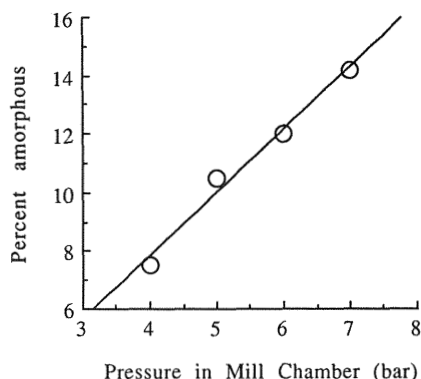


Fig. 19.6 Effect of applied pressure in a fluid energy mill on the amount of amorphous material produced. (Data from Briggner et al., 1994.)

SYMBOLS

- A = surface area of powder
 $C = E/\ln[d'/d'']$ = factor connecting energy input with particle size reduction during a milling process
 d' = weight mean diameter of particle population after milling
 d_b = average diameter of the milled particles
 d_a = mean particle diameter before milling
 E = energy input into a milling process
 f = cumulative fraction of particles larger than x
 g = gravitational acceleration
 K = milling rate constant = q_1/C
 k = milling rate constant
 M = mass (weight) of particles after time t of milling
 M_0 = mass of particles before milling
 N = number of particles (a) at time t , (b) after m or p rotations in a hammer mill
 N_0 = initial number of particles before milling
 m = number of impacts
 n = number of holes in a hammer mill screen
 P = percentage of material retained on a sieve size d' , where d' , as a function of milling time t
 p = number of impacts (between 0 and m)
 Q = coefficient in relation between energy and inverse diameter difference
 q_1 = coefficient connecting energy of milling to time of milling
 r = radius of a ball mill
 t = time of milling
 w = mass (weight) of material being milled
 w_a = weight of particles with diameter d_a = mass (weight) of material being milled with the original diameter
 w_b = weight of particles with diameter d_b
 x = particle size
 x_0 = initial particle size before milling in a hammer mill
 α_s = surface shape factor
 α_v = volumetric shape factor
 α = fraction of particles impacted in one rotation in a hammer mill
 α_2 = coefficient in equation relating energy input to diameter of hole in screen and number n of holes
 β_1 = Hooke's slope = strain/stress
 β_2 = surface energy
 β_3 = Weibull coefficient
 ϕ = Weibull exponent
 Γ = shape factor = d times area/volume = α_s/α_v
 λ = exponent in equation relating energy input to diameter of hole in screen and number n of holes
 ω = rotations speed in radians
 τ = residence time in mill

REFERENCES

- Adolfsson A, Caramella C, Nyström C (1998). *Int J Pharm* 160:187.
- Arias MJ, Moyano JR, Gines JM (1997). *Int J Pharm* 153:181.
- Austin LG (1971/1972). *Powder Technol* 5:1.
- Austin LG, Trimarchi T, Weymont NP (1977). *Powder Technol* 17:109.
- Briggner L-E, Buckton G, Bystrom K, Darcy P (1994). *Int J Pharm* 105:125.
- Carstensen JT (1993). *Pharmaceutical Principles of Solid Dosage Forms*. Technomic Publishing, Lancaster, PA, p 51.
- Carstensen JT, Patel MR (1974). *J Pharm Sci* 63:1494.
- Carstensen JT, Puisieux F, Mehta A, Zoglio MA (1978). *Int J Pharm* 1:65.
- Gardner RP, Austin LG (1975). *Powder Technol* 12:65.
- Gardner RP, Rogers RS (1975). *Powder Technol* 12:247.
- Harwood CF, Pilpel N (1968). *J Pharm Sci* 57:478.
- Jindal VK, Austin LG (1976). *Powder Technol* 14:35.
- Kigasawa K, Maruyama K, Tanaka M, Watabe K, Kooyama O (1981). *Yakugaku Zasshi* 101:733.
- Koh IB, Shin SC, Lee YB (1986a). *Arch Pharm Res* 9:55.
- Koh IB, Shin SC, Lee YB (1986b). *J Korean Pharm Sci* 16:36.
- Mehta A, Adams K, Zoglio MA, Carstensen JT (1977). *J Pharm Sci* 66:1462.
- Nakai Y, Nakajima K, Yamamoto K, Terada K, Konno T (1978). *Chem Pharm Bull* 26:3419.
- Mitrevej A, Sinchaipanid N, Junyaprasert V, Warintournuwat L (1996). *Drug Dev Ind Pharm* 22:1237.
- Shin S-C, Oh I-J, Lee Y-B, Choi H-K, Choi J-S (1998). *Int J Pharm* 175:17.
- Steendam R, Lerk CF (1998). *Int J Pharm* 175:33.
- Steiner G, Patel MR, Carsensen JT (1974). *J Pharm Sci* 63:1395.
- Yamaguchi G, Sakamoto K (1959). *Bull Chem Soc Jpn* 32:1364.
- Yamamoto K, Nakano M, Arita T, Nakai Y (1974). *J Pharmacokinet Biopharm* 2:487.
- Yamamoto K, Nakano M, Arita T, Takayama Y, Nakai Y (1976). *J Pharm Sci* 65:1484.
- Zhang Y, Johnson KC (1997). *Int J Pharm* 154:179.

RECOMMENDED READING

- Lantz RJ Jr (1981). In: Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms*, vol. 2. Marcel Dekker, New York, pp 77-152.
- Parrot EL (1986). In: Lachman L, Lieberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Lea & Febiger, Philadelphia, pp 21-47.

Blending

20.1. Statistics of Ideal Mixtures	336
20.2. Modes of Sampling	338
20.3. Segregation of Noncohesive Powders	340
20.4. Mixing of Noncohesive Powders	341
20.5. Blending Principles	342
20.6. Kinetics of the Noncohesive Mixing Process	343
20.7. Premixing	346
20.8. Effect of Particle Size	347
20.9. Mixing Efficiency	347
20.10. Ordered (Cohesive) Mixing	348
Symbols	351
References	352
Recommended Reading	352

There are no solid dosage forms (except sachets) that are one-component systems. The material to follow will concentrate on binary systems, but the findings may also be extrapolated to multinary systems. Whether or not the final dosage form is a tablet, a capsule, or a powder, all go through a stage in which the product exists as a powder mixture.

As such, it is desirable that the mixture be “uniform,” and the means by which this is assessed is by taking samples from various spots in the assembly, assaying these, and judging the “goodness of mix,” the “completeness of mix,” or “the degree of mixing,” by way of comparing the results with (a) the theoretical mean x , of the mixture, and (b) the standard deviation.

Ideally, all the samples would contain a fraction x of drug and have a zero standard deviation, and this, hypothetical situation, is referred to as an “ideal mixture” in the following.

First, however, a note on how degrees of blending are assessed, by sampling.

20.1. STATISTICS OF IDEAL MIXTURES

Assume an ideal mixture of noncohesive particles, as shown in Fig. 20.1. The mixture contains a fractional one-quarter of drug (dark circles) and three-quarters of excipient (light circles).

To illustrate the theoretical effect of sampling (ϵ_s), suppose the sample were taken one particle at a time, and that the sample size was 4. The probability of picking a drug particle would be one-quarter, so that, for example, the probability of picking four drug particles one after another would be $(1/4) \times (1/4) \times (1/4) \times (1/4) = 0.0039$ or 0.39%. The probability of picking the first particle as a drug particle and the next three as excipients (i.e., D-E-E-E) would be $(1/4) \times (3/4) \times (3/4) \times (3/4) = 0.105469$. However, a sample containing one drug particle could also be obtained as E-D-E-E, or E-E-D-E, or E-E-E-D, so that the probability of obtaining one drug particle would be four times 0.105469 (i.e., = 0.422). The factor “4” is the number of ways one particle can be taken from a set of four and is denoted combinatorial 4 over 1, symbolically written here as $\{^4_1\}$. In general the number of ways n items may be removed from a total of N items is given by combinatorial N over n , given by:

$$\{N_n\} = N! / \{(N - n)!n!\} \quad (20.1)$$

Examplewise $\{^4_1\} = 4 \times 3 \times 2 \times 1 / (3 \times 2 \times 1)(1) = 4$, as enumerated physically in following.

When the combination containing two of each comes up, the question is how many ways can this be done (i.e., how many combinations of 2 *E*s and 2 *D*s are there). This number would be given by

$$\{^4_2\} = 4! / \{2!2!\} = 6 \text{ ways} \quad (20.2)$$

It is an oddity, that

$$0! = 1 \quad (20.3)$$

This will simply be accepted, and not explained here. The total number of possibilities follow.

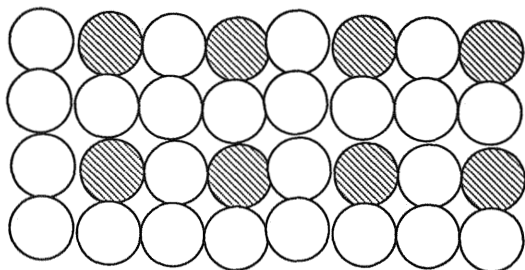


Fig. 20.1 Perfectly blended spheres of equal size.

$$0 \text{ drug particles } \{^40\}(0.75)^4 = 0.3164 \text{ of the time} \quad (20.4)$$

$$1 \text{ drug particle } \{^41\}(0.25)(0.75)^3 = 0.4220 \text{ of the time} \quad (20.5)$$

$$2 \text{ drug particles } \{^42\}(0.25)^2(0.75)^2 = 0.2108 \text{ of the time} \quad (20.6)$$

$$3 \text{ drug particles } \{^43\}(0.25)^3(0.75) = 0.0469 \text{ of the time} \quad (20.7)$$

$$4 \text{ drug particles } \{^44\}(0.25)^4 = 0.0039 \text{ of the time} \quad (20.8)$$

The numbers add up to 1.00 as they should (one would obtain either no, one, two, or three drug particles in a sample, and that accounts for all the possibilities).

In general the probability of obtaining n drug particles, from a sample of N particles containing x fraction of drug, would be

$$\Pr(x, N, n) = \{N_n\}x^n(1-x)^{(N-n)} \quad (20.9)$$

The distribution of Eq. (20.9) is known as the binomial distribution. For large numbers of N it will approximate a normal distribution. *The point here is that the assay one obtains from random sampling is a function of the sample size.*

The mean $\bar{x}$, variance s^2 , and standard deviation s , of the distribution [see Eq. (20.9)] are

$$\bar{x}_{\text{avg}} = x \quad (20.10)$$

$$s^2 = N(1-x)x \quad (20.11)$$

$$s = [N(1-x)x]^{1/2} \quad (20.12)$$

The standard deviation is the square root of Eq. (20.11), and the relative standard deviation (rsd), a term employed often in blending science, is the expression in Eq. (20.12) divided by Nx (the average number of particles in the mixture); that is,

$$\text{rsd} = 100[(1-x)/(Nx)]^{1/2}\%, \quad (20.13)$$

the factor 100 stemming from the fact that rsd values are usually expressed in percent.

It is noted that the foregoing holds for an ideal mixture, and that the *rsd in Eq. (20.6) is the smallest possible standard deviation that may be expected by sampling a mixture*. Since N is usually large, this is approximately zero, but some dosage forms (e.g., sustained-release pellets), may have a limited number of particles per dose, so that in such situations the relative standard deviation attributable to probability (ϵ_C) may be rather large.

As an example, one might ask what the smallest number of particles that may be used in a sustained dosage form with $x = 0.10$ fraction drug (and the remaining particles being blanks of the same size) and have it still meet USP requirements ($\text{rsd} = 6\%$).

The answer to this is that the smallest number is given by Eq. (20.13), that

$$6 = 100[0.9/0.1N]^{1/2} \quad (20.14)$$

So that

$$N = 250 \quad (20.15)$$

20.2. MODES OF SAMPLING

In blending experiments the type of sampling always involves removing specimens from different parts of a mixer and assaying them. In model experiments with blending in a barrel-roller, Patel (1975) and Carstensen and Patel (1975) employed a barrel that was cut down the middle, so that the two parts could be taken apart (Fig. 20.2A and B). Two powders were then carefully placed in each end of the bottom trough, the lid put on, and the material blended for a certain time. The top lid was then removed and replaced with a lid that had ten partitions in it (see Fig. 20.2C). The blending process and replacement are shown “flat” in Fig. 20.2D, E, and F. The cylinder was then rotated 180° (Fig. 20.2G) at which point ten fractions could be harvested and assayed, and in this way, the blending process could be followed as a function of time.

Rather than using the divided upper lid, some investigators have used the technique of pouring molten wax into a powder mixture, letting it set up, and dividing the wax slab by cutting it into appropriate pieces. In that manner “samples” at varying distances (or various spots in, for example, a larger blender) may be assayed.

In the foregoing setup (which is for experiments) the entire mix may be sampled. For larger-type blenders and in situations during which small samples are taken, a thief is most often used. This (Fig. 20.3) consists of two concentric cylinders, one with a larger diameter than the other. The inner cylinder has one (or more) cavities of the desired size (the sample size), and the outer cylinder has a hole at the same level. If the holes are not aligned, the thief may be lowered into the mixer to the desired spot. At this point the inner cylinder is rotated, so that the cavity is aligned with the hole, and in this manner powder may flow into the cavity. By rotating the inner cylinder 180° again, the thief is “closed,” it can be retracted, and the sample collected and assayed.

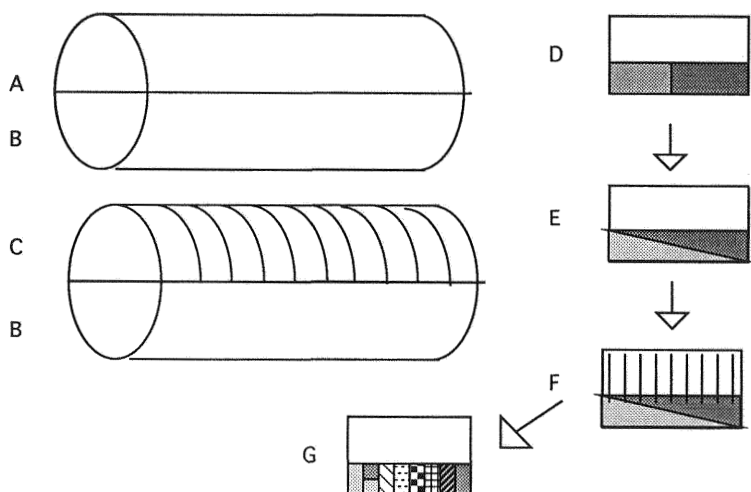


Fig. 20.2 Sampling device for model study of barrel rolling used by Patel (1975).

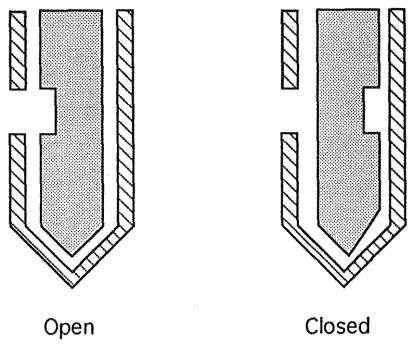


Fig. 20.3 Principle of thief side-port sampler.

The sample size is dependent on the size of the cavity, and in certain thieves there is a large cavity, into which fits a similar volume plug with a smaller cavity. In that manner the same thief may be used for many sample sizes.

Thieves with multiple holes also exist, but have certain disadvantages, to be discussed later.

For cohesive powders (to be covered shortly), an end-thief may be used. However, for cohesive powders, dependent on ordered mixing (to be discussed in the following) the side-entry thief is not a good choice. Insertion of the thief will often rupture the bond between small, adhered particle, so that the powder will unmix at the point of insertion of the thief. Hence, the sample taken, will not be representative of the mixture.

Cohesive powders form “plugs.” The principle of a thief fairly adequate for cohesive powders is shown in Fig. 20.4. The thief is lowered with the outer cylinder flush with the bottom of the inner cylinder. At the appropriate (sampling) location, the inner cylinder is arrested, and the outer sleeve is lowered further, encasing a certain amount of powder. As this is cohesive it will not “fall out,” when the thief is retracted. The sample can then be harvested after the thief is completely out of the mixture. The sample size depends on the difference in position of the outside sleeve and the bottom of the inner cylinder at the point of sampling.

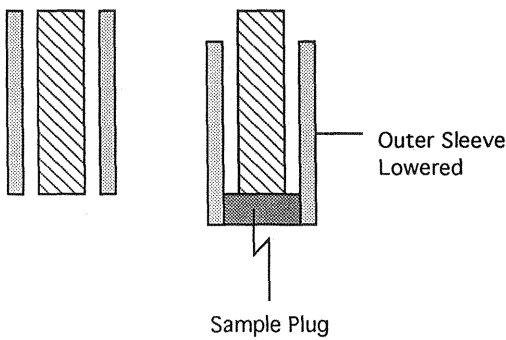


Fig. 20.4 Schematic of a plug thief.

20.3. SEGREGATION OF NONCOHESIVE POWDERS

There are several types of blending: (a) noncohesive blending, (b) cohesive blending, and (c) ordered blending. In a manner of speaking, type (c) is a subdivision of (b). On the other hand, (a) is never noncohesive, for some cohesion is always at play, but for larger particles it is insignificant.

However, before discussing blending in detail, a short note on the opposite of blending (i.e., segregation) is in order. It is possible to perceive an arrangement of particles that is "completely blended" or "completely uniform," as long as the sample size is larger than the rational number that equals the ratio sum. For instance in the particles in Fig. 20.5, a sample size of four particles in square array would always be in a ratio of 3:1.

To assess what factors affected segregation, Olsen and Rippie (1964), and Rippie et al. (1964a,b) conducted experiments with steel balls. They would arrange a "completely mixed" assembly of steel balls of two types (e.g., two different diameters, two different colors), in a cylinder, and then vibrate the cylinder.

They showed, by perturbing these completely uniform populations that the spheres would separate, and that the standard deviation s of the population would approach an equilibrium s_∞ , i.e., that

$$s = s_\infty \{1 - e^{-k_s t}\} \quad (20.16)$$

where k_s is a segregation constant; this is shown in Fig. 20.6.

The equilibrium level is a function of the intensity of the perturbation (the energy input of the mixer). We learn, thereby, that from the point of view of noncohesive mixing, complete mixing is never possible, not only from a sampling point of view, but even under ideal-mixing conditions, there will always be a residual standard deviation, s_β , attributable to the mixing energy. Because, suppose, as visualized in the foregoing, that it would be possible in a mixer to attain "perfect mixing" at a given time point (Fig. 20.7). A microsecond after this geometry had been achieved, it would be disturbed by the mixer so that, to repeat, *a zero standard deviation is never attainable in practice.*

Rippie and co-workers also found that the rate constant k_s was a function of the volumes v_1 and v_2 of the balls, k_s being the larger the larger the difference between the two. The rate constant was also a function of the agitation intensity

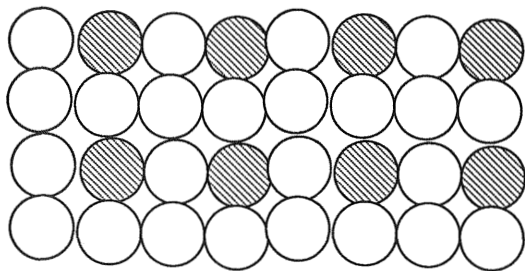


Fig. 20.5 Perfectly blended spheres of equal size.

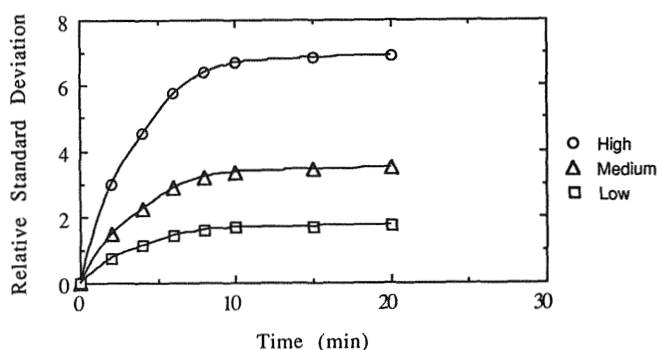


Fig. 20.6 Rippie's segregation experiment. (Data from Rippie, 1964a,b.)

(the energy input), and the equilibrium level, as well as the rate constants, were plottable by an "Arrhenius-type equation" using $1/\text{energy}$ (1 divided by amplitude of the vibration) as abscissa and $\ln[k_s]$ as ordinate.

20.4. MIXING OF NONCOHESIVE POWDERS

Obviously a mix will become randomized by way of the mixing action, and the final mixedness will be a function of the following:

1. The efficiency of the mixer in a positive sense, in that it will cause mixedness of a blend. The faster the material "mixes" the more efficient is the mixer.
2. The energy input, because the higher the energy input the higher will be the final standard deviation.
3. The sampling procedure. This, essentially, does not affect the mixing, but rather, the result, and will be discussed later.

The types of blenders most often used in pharmaceutical manufacturing are shown, schematically, in Fig. 20.8. The figure represents *principles*, in fact it represents common blenders in existence for the last 50 years. More modern blenders, however, are based on the same principle.

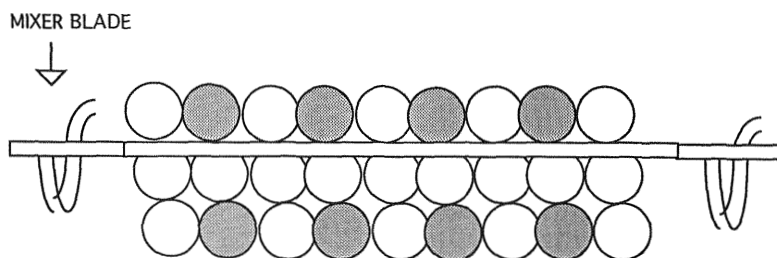


Fig. 20.7 A hypothetical 3:1 perfect blend in a ribbon blender.

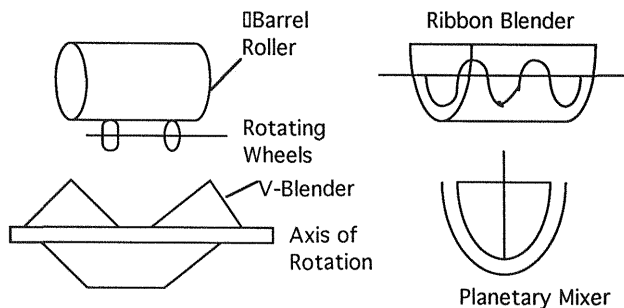


Fig. 20.8 Types of blenders.

20.5. BLENDING PRINCIPLES

In the following, only binary mixtures will be considered, but the principles arrived at are equally applicable to multinary mixes.

If two materials are placed in a mixer that is then started, they are then placed "on top of each other" (Fig. 20.9). At times layers are alternated, but the essence is that the two components lie in separate layer. To achieve blending, the particles must be separated (a sort of fluidization), and they must be allowed to pass one past the other. This is exemplified in Fig. 20.9.

A first necessary step is an expansion of the bed. This is one reason that one cannot "scale-up" capacities of mixers by simply determining the apparent density (ρ') and then multiply the volume V' of the mixer by ρ' to calculate the mass (weight) of particles that would fit in it. In any event, most manufacturing situations call for a "round" number of tablets (e.g., 2 million), so that the mixer may not be used to full capacity in any event. This in spite of industry's zest for cost-cutting, because the larger the batch, the more economical the operations as concerns assay and labor costs.

For the layers to assume a nondense configuration, a force must be applied that overcomes the cohesive force between particles. The motor driving the ribbon or blades that cause the blending provide the energy E necessary to separate the particles and to make them move across one another. The word "noncohesive" is a

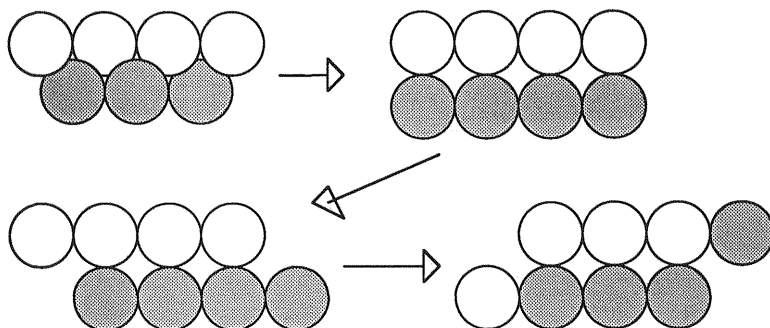


Fig. 20.9 Mode of noncohesive blending.

convenient misnomer, because there *is* cohesion at all times, so even in noncohesive blending there is the work associated with separation of the particles, but it is minimal. The work expended deals more with moving layers of particles across other layers, and this is where *frictional forces* have to be overcome. So cohesion and friction are of importance in mixing.

Cohesion is defined as the force c (small case) between two particles, and it is proportional to the mass of the particles and inversely proportional to the square of the distance between the two particles. Also, the smaller the particle the larger the cohesive stress. When the particles are fairly large (more than $50\text{ }\mu\text{m}$) then the cohesive stress is relatively small, and mixing such powders is referred to as *non-cohesive mixing*, and will be treated first.

20.6. KINETICS OF THE NONCOHESIVE MIXING PROCESS

Let us assume that mixing is to be carried out between two solid components, A and B (one of which could be a drug substance), and that there are two parts of A and one part of B. To ascertain that they were “completely mixed,” it would be necessary to sample in different parts of the mixer and assay them. For an ideal noncohesive mixing case the initial relative standard deviation will be given by the following argument.

The mixture shown in Fig. 20.10 is the 2:1 mixture described in the opening paragraph, but assume that it is a powder blend, in general, where there is a fraction x of A and a fraction $(1 - x)$ of B. If a thief is lowered at random at N points in the mixer, then a fraction x of the time (e.g., one-third of the time in the foregoing example); that is, Nx times, the thief would sample A and a fraction $(1 - x)$ of the time (e.g., two-thirds of the time in the foregoing example); that is, B would be sampled $N(1 - x)$ times. The average content is x , so samples counting only A, since their drug content would be 1.0, would differ from the mean by $1 - x$, and samples containing only B would differ from the mean by x (since their content is zero). Hence, the sum of squares Σ would be

$$\Sigma = N(1 - x)x^2 + Nx(1 - x)^2 = N(1 - x)x(x + 1 - x) = Nx(1 - x) \quad (20.17)$$

The number of degrees of freedom is $N - 1$, so that the variance is

$$s^2 = Nx(1 - x)/(N - 1) \approx x(1 - x) \quad (20.18)$$

if N is large, or, the standard deviation would be

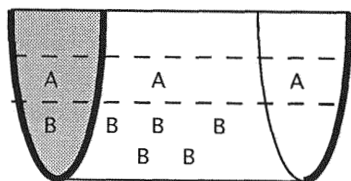


Fig. 20.10 Example of sampling positions before blending, in which component B is placed in the mixer first, and then A. Sampling is never carried out at $t = 0$ and the figure is simply shown to demonstrate what the initial standard deviation *would* be.

$$s_0 = [Nx(1 - x)/(N - 1)]^{1/2} \quad (20.19)$$

Here, N is the number of samples taken. Regulations, nowadays, employ the relative standard deviation, rsd , which is:

$$rsd = 100s/x$$

so that the “initial” rsd is:

$$rsd_0 = 100[N(1 - x)/(N - 1)x]^{1/2} \quad (20.20)$$

If it is assumed that the rsd decreases to a limiting value and that this final rsd is governed by sampling error only, then it is dictated by a binomial distribution, that

$$s_0 = 100[Nx(1 - x)/(N - 1)]^{1/2} \quad (20.21)$$

It is of importance to know what the final condition is and how fast one arrives at it. From theory it can be shown that the final standard deviation of the binomial distribution is given by

$$s_\infty = \{(1 - x)/xn\}^{1/2} \quad (20.22)$$

where n is the number of particles in question; the complete blending equation is given by:

$$\ln[(s - s_\infty)/(s_0 - s_\infty)] = -kt \quad (20.23)$$

or

$$s = s_\infty + (s_0 - s_\infty) \exp(-kt) \quad (20.24)$$

But aside from this there is the standard deviation attributed by the energy input of the mixer, so that the final standard deviation will be

$$s_\infty^2 = s_{\text{binomial}}^2 + s_{\text{energy}}^2 \quad (20.25)$$

It suffices to say that the relative standard deviation will approach some finite number, in which one of the factors that plays a role is the energy input in the mixer.

k is the so-called blending constant. The larger it is, the more efficient is the blending. When s_∞ is small, which is the case even when the particles are moderately small (i.e., the number of particles in the sample is large), Eq. (20.24) simply becomes

$$s = s_0 \exp(-kt) \quad (20.26)$$

and Eq. (20.23) becomes:

$$\ln[s/s_\infty] = -kt \quad (20.27)$$

This is what will be assumed in the following. A point should be made, however, of the influence of Eq. (20.22). The “allowed” standard deviation in blending sampling, which is of sample size of 1–3 times dose weight, is 5%. Equation (20.22), as a consequence, limits to a lower limit the number of particles that a dosage form may contain. For general dosage forms (immediate-release capsules and tablets), n is quite large, but for sustained-release pellets it may be rather small.

Calculations should, therefore, always be made with Eq. (20.22) to ascertain that the particle size of the product (i.e. the number of particles in the dosage form) is larger than the minimum dictated by the equation.

As an example of mixing kinetics, consider the data in Table 20.1. This is a 2:1 powder mix, and the initial *rsd*, by the foregoing, should be

$$s_0(2:1) = 100\{9(1/3)(2/3)/8\} = 50$$

(20.28)

The table shows the individual assays at nine points in a mixer as a function of time. When these are plotted versus time, Fig. 20.11 results, and when the logarithm of the standard deviation is plotted versus time, Fig. 20.12 results.

The blending rate constants *k* are a function of the fractions, *x* and (1 − *x*) of the two components. The reason for this, and its qualitative consequences, are dealt with in the following.

An extremum in the initial variance [(see Eq. (20.18))] occurs when ∂[*s*²]/∂*x* = 1 − 2*x* = 0, that is, when *x* = 1/2. The functions *x*(1 − *x*) and (1 − *x*)/*x* are shown in Fig. 20.13.

Table 20.1 Standard Deviations of a 2:1 Powder Mix as a Function of Mixing Time

Sample position	Time = 0	Time = 1.5 min	Time = 6.6 min	Time = 15 min
1	0	10	5	65
2	100	90	95	68
3	0	70	30	68
4	100	80	70	66
5	0	60	40	61
6	100	40	90	63
7	100	85	96	69
8	100	90	84	72
9	100	75	90	69
Avg	66.6	66.6	66.7	67.0
RSD	50	33.4	12.2	3.4

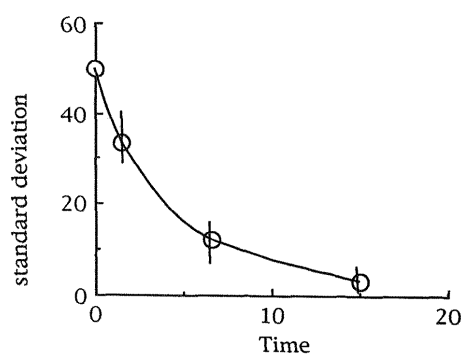


Fig. 20.11 Data from Table 20.1 plotted as shown in Eq. (20.26).

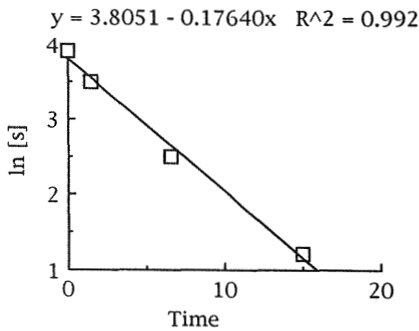


Fig. 20.12 Plot of figures in Table 20.1 plotted as a function of Eq. (20.2).

20.7. PREMIXING

For the reasons shown in Eq. 20.22 it is obvious that for compositions in which the drug concentration is very low, the blending may cause a problem. Consequently, premixing is often resorted to. The concept of *geometric mixing* is an old concept and has its roots in the fact that in compounding, where strong mixing was not available, it was customary to take one part of drug substance and mix it with one part of excipient. To these two parts of premix were added two parts of excipient to form premix 2, and so on until all was blended.

This is not practical on an industrial scale, so it is a general practice to make *one premix* (not a geometric number of premixes) and make it in a ratio that is convenient with available equipment. It is usually carried out in barrel rollers, so that the ratio of the premix would be approximately two-thirds the volume of the drum to 90% of the volume of the final mixer.

The principle of geometric mixing is the belief that a 50:50 mix is the “easiest” (i.e., can be mixed most completely) and is the fastest to mix (and most convenient to handle in the initial steps). If this were true, then the rate constant would be maximum at $x = 0.5$, and it can be shown that, under such circumstances, the best amount of *premix* to employ would be given by $\{x\}^{1/2}$. For instance if $x = 0.16$, then the premix should be a total of $\{0.16\}^{1/2} = 0.4$, so that for a 100-kg batch, the 16 kg of drug substance would be mixed with 24 kg of excipient (to make a total of 40 kg), and this preblend then mixed with the remaining 60 kg of excipient.

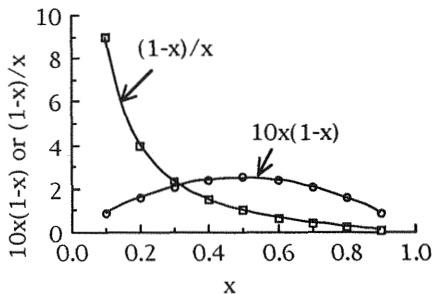


Fig. 20.13 Traces of the functions $x(1-x)$ and $(1-x)x$.

20.8. EFFECT OF PARTICLE SIZE

So far, the mixing process discussed has concerned itself with the blending of *mono-disperse*, *binary* mixtures. There is, however, a significant influence of particle size on mixing.

Patel (1978) and Carstensen and Patel (1977) have shown the following:

1. If particles are of equal size (Fig. 20.14a), mixing is fast and complete, and segregation very slow, if not nonexistent. This depends on the surface roughness of both compounds to be of equal effect.
2. If particles are of different sizes and particles of A do not fit in the interstices of B (see Fig. 20.14b; i.e., does not percolate) or vice versa, then mixing is exceedingly slow, if not nonexistent.
3. If particles are of different sizes and particles of A can percolate in the interstices (see Fig. 20.14c) then blending is fast, but *segregation* is also fast.

Relative to point 3, it should be noted that the degree of segregation is a function of x and the smaller particle diameter(s). If they are such that maximum density has been reached (the interstices are just filled), then segregation will not occur, and the closer the particle population is to such a state, the more stable the powder mix.

20.9. MIXING EFFICIENCY

From what has been described about cohesion, it is seen that sufficient force or energy must reach all particles so that they may be separated. It is overcoming of the cohesion in powders (and this is particularly true about cohesive mixing, to be discussed shortly) that gave rise to the development of so-called high-shear mixers. In these there are slow-moving blades (paddles, impellers; Fig. 20.15A) and a fast-moving chopper (see Fig. 20.15B).

The powder that passes the choppers will have the cohesive stress overcome (i.e., the particles will separate), and the blades A, with much less energetic mixing,

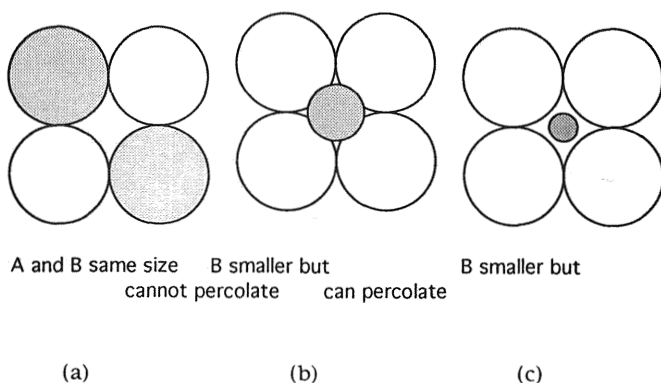


Fig. 20.14 Influence on particle size by mixing. (Data from Patel, 1978.)

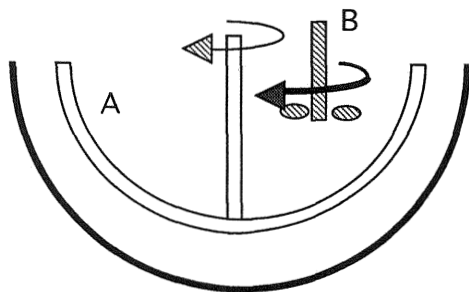


Fig. 20.15 Principle of a high-shear blender.

will allow the now separated particles to mix. What is needed is that the blending situation is such that all the particles will pass by the choppers, B.

Because, when the choppers are on, the energy input is high, it will give rise to a high residual *rsd*, so that the last part of the blending should be carried out with the choppers off.

20.10. ORDERED (COHESIVE) MIXING

Historically, ordered *mixing or interactive mixtures* was first introduced as a concept by Hersey (1975). The way in which drug adheres to a carrier is by electrical forces, by capillary interaction resulting from liquid bridges between drug and carrier (wet granulation), and by solid bridging (Rumpf, 1961; Krupp, 1967; Zimon, 1982). It is the latter that is, commonly, referred to as *ordered mixing*.

The previous sections of the chapter have been concerned with “noncohesive” mixing, with the understanding that noncohesiveness implies that the cohesion is small. Cohesion becomes more important as the particles become smaller [see Eq. (17.2) and (17.3)], and this means slower mixing and, depending on the situation, less complete mixing. When the particles of one component are small compared with the other, situation 3 occurs as described in the foregoing, but when the smaller particle becomes *much* smaller than the large particle, the small particle may attach itself in a rather permanent fashion to the larger particle. This gives rise to a desirable situation denoted *ordered mixing*, or interactive mixing. Some comments on it are in order before describing its origin and usefulness.

There is, as has been mentioned in Chap. 17, proportionality between cohesive force and particle diameter, and the force between particles is inversely proportional to the distance between their centers. Equations (17.2) and (17.3) are repeated here for convenience. Reference is made to Fig. 20.16. The cohesive force exerted upon the small particle is

$$C = \beta d_1^3 d_2^3 \quad (17.2)$$

where d_1 is the diameter of the small particle, and d_2 that of the large particle. The force is inversely proportional to the central distance squared; that is, the force on the smaller particle is

$$F = \beta' / (d_1 + d_2)^2 \quad (20.29)$$

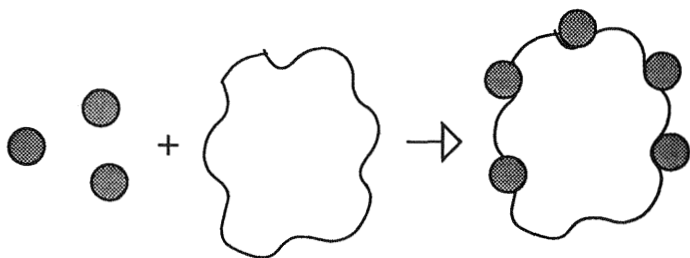


Fig. 20.16 Formation of an ordered mix.

so that the total force on the smaller particle is

$$F_{\text{total}} = \beta' d_1^3 d_2^3 / (d_1 + d_2)^2 \approx \beta' d_1^3 d_2 \quad (20.30)$$

in cases where $d_1 \ll d_2$. The force works on a surface area equal to the cross section of the smaller particle, so that the stress is

$$c_2 = \beta' d_1^3 d_2 / (\pi d_2^2) = \beta' d_1^3 / (\pi d_2) \quad (20.31)$$

that is, the stress is larger, the smaller the small particle. When particles used are in the micron region, and the large particles are fairly large, the small particles may attach themselves to the larger particles and remain there, unless a stress larger than that shown in Eq. (20.31) is exerted on them.

This stress may occur in certain situations. One such is the use of a side-entry thief for sampling such powders, and this has been a reason for unreasonably high standard deviation values for certain powders of this nature and for such powders other thieves (e.g., the plug type thief shown in Fig. 20.4) are appropriate.

Thieves should always be *validated* before deemed appropriate for sampling of a certain powder. This can be done fairly easily. If a small batch is made, or if a drum is collected from a larger batch and barrel-rolled to some degree of uniformity, then one-quarter of the drum may be transferred to another drum (Fig. 20.17).

Samples are now taken at three designated spots on the surface, and transfer repeated with another one-quarter of the content of the first drum, so that the second is now half-full. The transfers must be carried out, using a large scoop, and carefully, so layers are not disturbed. Sampling by spoon is now done in three spots in the half-full drum, and this is repeated in the subsequent three-quarters-full drum. The drum is then filled up.

The samples taken by spoon are nonperturbed, because the spoon does not (or only very minimally) disturb the powder mass. The thief to be tested is now inserted into the powder in the appropriate places: to the bottom layer first, then to the second layer, and then the third layer, care being taken to take the samples in the same spots that the spoon samples were taken.

The results should be identical, or at best the standard deviations obtained should be the same, if the thief does not perturb the mixture during the sampling.

The other situation is when certain "rugorous" excipients are used. York has reported on the adverse effect of pregelatinized starch on ordered mixes on spray-dried lactose.

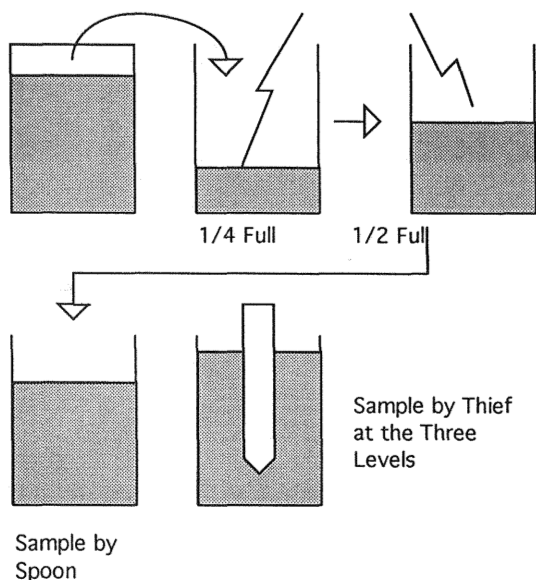


Fig. 20.17 Validation of a thief.

Staniforth (1980), has described techniques for making dendritic spherulites of sugars (e.g., fructose, lactose, or mannitol), by recrystallization under high pressure.

The capability of “holding” fine (micronized) material will depend on the surface area that is accessible to the adherent fines, and are shown, by comparison with other direct compression ingredients, in Table 20.2

The most common, and most efficient excipient for making ordered mixes is a grade of spray-dried lactose known as Flo-Fast. As depicted in Fig. 20.16, it is desirable that the larger particles have crevices into which the fines may fit, and the surface of Flo-Fast has, under scanning electron microscopy, exactly such a moon-like appearance. Granular dicalcium phosphate also possesses this attribute to some degree, whereas microcrystalline cellulose has a smoother surface and, hence, lends itself less to order mixes.

Ni (1981) showed that glyberide would have to be fine enough to have a surface area of $3.5 \text{ m}^2/\text{g}$ to make satisfactory ordered mixes with spray-dried lactose

Table 20.2 Ordered Mixes and Surface Areas

Excipient	Surface area available ($> 2 \mu\text{m}$)	Surface area available ($> 10 \mu\text{m}$)
Dipac (Sucrose)	817	—
Emdex	1985	—
Crystalline lactose	4848	583

Table 20.3 Estimates from Repose Angles of Quality of Excipients to Form Ordered Mixes

Composition	Repose angle (°)	Comment
Trimethozin < 4 μm	41.5	
Crystalline lactose < 160 μm	48.1	
Spray-dried lactose (SD)	39.9	
Crystalline lactose + trimethozin	42.9	about = α of trimethozin
Spray-dried lactose + trimethozin	40.0	about = α of SD lactose

Source: Kata, 1979.

Kata (1979) estimated the quality of excipients to form ordered mixes by determining repose angles α of their mixes. Kata’s data are shown in Table 20.3.

It is seen that when the drug is added to crystalline lactose, the repose angle implies that there is no difference between this composition and that of pure drug. But when the drug is added to spray-dried lactose, then the repose angle becomes identical with that of spray-dried lactose, implying that the drug is imbedded in crevices in the surface of the excipient.

Aspects of ordered mixing impinge on content uniformity of drug products, and there are reports in literature on the effect of particle size on blend uniformity (e.g., Yalkowsky and Bolton, 1990). In ordered blending, it is to be expected that the content uniformity would be better than in noncohesive blending, once the blend has been established. Yalkowsky and Bolton (1990) point out that when it is simply mechanical (van der Waal) forces that keep the small particle on the large particle, then attrition may affect uniformity, and in rigorous blending, segregation may occur; however, with prudent processing, the content uniformity should be favorable for such situations.

Zhang and Johnson (1997) prepared blends that contained 0.01 mg of drug per 99 mg of carrier. The carrier was a mixture of microcrystalline cellulose, dibasic calcium phosphate, and sodium starch glycolate that had been passed through an 80-mesh screen, and the drug substance was either of a 6- or 18-μm diameter. The coarser powder, when sampled in the official manner, had an assay of 88–130% and the coarser powder was 97–102%. This, essentially, shows the effect of particle size on the force between the smaller and larger particles.

Supabhol and Stewart (1996) have shown interactive mixtures of micronized diazepam with the following direct compression ingredients: compactrol, dicalcium phosphate (emcompress), and granules made by starch–lactose–povidone. The strength of the interaction was established by using compression in a Wood’s disk and rotation between 25 and 2000 RPM, and, for diazepam, 1 and 15% concentrations.

SYMBOLS

- C = cohesional force on a smaller particle
- d_1 = diameter of a smaller particle
- d_2 = diameter of a larger particle

F = force between two particles of unequal size

k = blending rate constant

k_s = segregation constant

N = number of samples taken in a powder before blending

$\{N_n\}$ = N combinatorial n (i.e., the number of ways of removing n drug particles from a total of N particles when sequence of selection is immaterial)

n = number of particles in a sample

$\text{Pr}(x, N, n)$ = probability of taking a sample of n drug particles from a total of N particles from a sample containing a fraction x of drug, when sequence of selection is immaterial

s = standard deviation of a noncohesive blend at time t

s_0 = standard deviation of a powder before blending

s_∞ = standard deviation of a noncohesive blend after infinite time

s_{energy^2} = residual variance of a blend caused by energy perturbation

t = time

x = fraction of drug

x_{avg} = fraction of drug content in a blend or a population

α = repose angle

β' = constant relating particle size to cohesional force

Σ = sum of squares

REFERENCES

- Carstensen JT, Patel MR (1977). *Powder Technol* 17:273.
- Kata M (1979). *Acta Pharm Technol* 25:203.
- Krupp H (1967). *Adv Colloidal Interface Sci* 1:11.
- Ni PF (1981). U. S. patent 4,916,163.
- Olsen JL, Rippie EG (1964). *J Pharm Sci* 53:147.
- Patel MR (1978). PhD dissertation. University of Wisconsin, Madison WI, p 15.
- Rippie EG, Olsen JL, Faiman MD (1964a). *J Pharm Sci* 53:1360.
- Rippie EG, Faiman MD, Pramoda MK (1967b). *J Pharm Sci* 56:1523.
- Rumpf H (1961). The Strength of Granules and Agglomerates. In: Knepper WA, ed. *Agglomeration*. Interscience, New York, pp 379–414.
- Staniforth JN (1980). U. S. patent 4,349,542 (issued 1982).
- Soebagyo SS, Stewart PJ (1985). *Int J Pharm* 25:227.
- Soebagyo SS, Stewart PJ (1990). *Int J Pharm* 66:263.
- Soebagyo SS, Stewart PJ (1993). *Int J Pharm* 91:227.
- Supabhol R, Stewart RJ (1996). *J Pharm Pharmacol* 48:1249.
- Zimon AD (1982). *Adhesion of Dust and Powder*, 2nd ed. Consultants Bureau, New York, pp 93–144.

RECOMMENDED READING

- Lantz RJ, Schwartz JB (1981). In: Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms*, vol 2. Marcel Dekker, New York, pp 1–52.
- Rippie E (1986). In Lachman L, Lieberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Lea & Febiger, Philadelphia, pp 3–21.

21

Wet Granulation

21.1. Equipment	354
21.2. Materials and Methods	354
21.3. Granule Measurements and Properties	356
21.4. Physics of the Process	358
21.5. Granulation Endpoints	358
21.6. Granule Density and Porosity	359
21.7. Extragranular Porosity	362
21.8. Use of Fluid Bed Granulation	364
21.9. Pellets	366
21.10. Granule Size Determination (Sieve Test)	367
21.11. Dissolution from Wet-Processed Granules	368
21.12. Spheronization	370
Symbols	370
Recommended Reading	371
References	372

Particle sizes are often too small to allow good processing into tablets or capsules. Earlier chapters have shown, for instance, that flow can be affected. Dissolution of dosage forms is also affected in a positive way, in that it is more rapid from a large surface area. The first step in dissolution, however, is wetting the surface, and hydrophobic drugs will not wet down easily. The larger the surface, the more difficult (the slower) will the wetting be. These are two reasons for *wet-granulating* powders for further solids processing. One more reason is that the process, which essentially consists of “gluing” particles together, also aids in forming bonds in tablets, in

which case, the granulating agent is referred to as a *binder*. Hence, there are three main purposes in wet granulating:

1. Particle enlargement
2. Increasing wettability
3. Adding binder to the particulate solid

21.1. EQUIPMENT

It has been noted, for instance in the introduction, that this text does not emphasize the actual machinery involved in solids manufacturing, and that the reader interested in the intricacies of equipment used, for instance, that in wet granulation, are referred to texts such as those listed under *Recommended Reading* at the end of this chapter.

Wet granulation can be carried out in kneaders. Most often, nowadays, these will include both an impeller and a chopper, so that mixing can be achieved at high intensity in a small area of the mixer, and the “feeding” of all the material into and about the chopper can be assured by the impeller.

Wet granulation can also be accomplished by (a) extrusion or (b) pelletizing, which may be carried out in rotary processors by wet granulation.

The wet granules are dried by various means, fluid bed drying being the most common.

21.2. MATERIALS AND METHODS

The principle of wet granulation is to add the binder by some means so that it will form bridges between the particles to form granules (Fig. 21.1).

As seen in Fig. 21.1 the general method is that

1. The binder is dissolved in the water (or solvent).
2. The powders are mixed.
3. The solution of binder (the granulating solution) is added.
4. After a suitable length of time, the wet granule has formed.

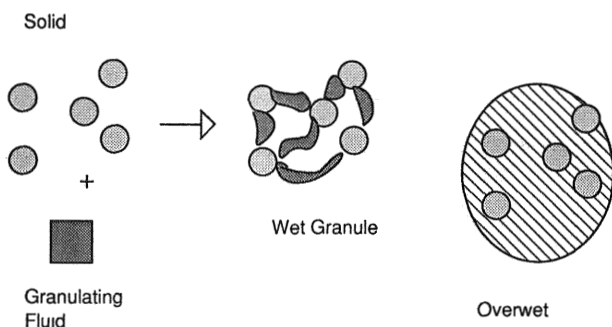


Fig. 21.1 Stages in granule formation.

Alternatively, the binder may be mixed with the powder, and solvent, or water (whichever is applicable), is added. There are several variables that must be established during the formulation, namely:

1. The amount of binder
2. The volume of granulating liquid
3. The length of time the mixture is mixed

The general method for doing this is shown in the flowsheet in Fig. 21.2.

The granulating fluid is added to the powder, which eventually forms what is denoted “wet granules” in Fig. 21.3. This corresponds to what is usually denoted a wet *funicular* structure (Newitt and Conway, 1958). If more water is added, then the liquid fills up most of the void space between the particles, and this is denoted a wet *capillary* structure. When all the void space (and even more) is occupied by granulating liquid, the granulation is overwet, and the structure is denoted a *droplet*.

For traditional granules, a porous structure is desired, and the granule should break or distort during compression. Because, during the process, the granule, after it is dried, is bound together by binder, usually in an amorphous state, the drying temperature is of importance, as is the final moisture content. A moisture content that is too low will cause the granules to become so brittle that they will break before the actual compression step, so that, when tableted, “cappers” may form. Too many fines will also affect the flow rates and uniformity of the ensuing tablet.

Adding somewhat too much water will cause an overwet granule (see Fig. 21.1), and this, after drying, will become very hard. At times this is desirable, but in such cases, pelletization (to be covered shortly), is the method of choice.

Many polymers, natural, modified, or synthetic, may be used as binders, or granulation agents, in the formation of granules. Chowhan and Palagyi (1978) and Chowhan (1980), for instance demonstrates the use of hydroxypropyl methylcellulose (HPMC) as a granulating agent (binder). This will be discussed further later. Some common binders are

Acacia
Ethyl cellulose (EC)
Methylcellulose (MC)
Hydroxypropyl methylcellulose (HPMC)
Hydroxypropyl cellulose (HPC)

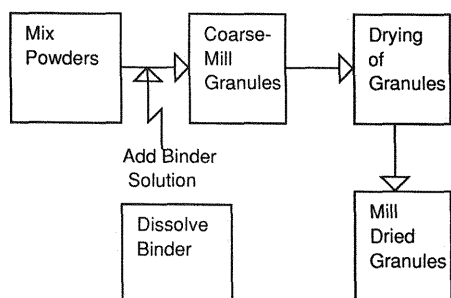


Fig. 21.2 Flow sheet for granule production.

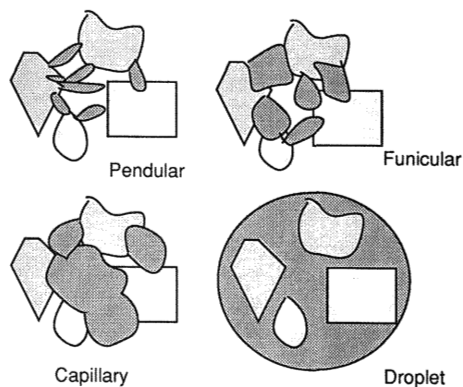


Fig. 21.3 Various types of granules created by the type of granulation and the granulation time.

Polyvinylpyrrolidone (PVP)

Starch

To this list it is possible to add, for instance, gelatin and pregelatinized starch. Some of the binders mentioned (e.g., ethyl cellulose) are only solvent soluble, some both water and solvent soluble; however, starch is only water soluble. Starch has to be added to boiling water (e.g., in a ratio of 1:10) to form a gel. The process for producing a wet mass is as shown in Fig. 21.1.

In recent years, the synthetic and cellulose derivative binders have been preferred; for instance, Durrani et al. (1997) have described the use of Klucel EF (HPC) and Carbopol 934P for wet granulation.

HPMC has been used for wet granulation by several investigators (Nagy et al., 1980; Gudsoorkar and Khanna, 1980). Krycer et al. (1983) made tablets of HPMC by dissolving it to 8% in water, and granulating it to a total HPMC concentration of 3% w/w. Rak and Chalabala (1975), used 1000 g of methylcellulose (0.5% in solution) in a total of 3000 (dry) g of (wet) granulation (i.e., a total concentration of 0.17%) and ten times as much in a second set-up (i.e., Methocel can be used in small percentages in wet granulation).

Chowhan and Chow (1981) and Chowhan and Palagyi (1978) have wet granulated naproxen with HPMC. Chowhan (1980) has used HPMC in wet granulation of salicylic acid tablets.

Shotton and Edwards (1974) used 4% methylcellulose as a binder in wet granulation of sulfadiazine tablets.

21.3. GRANULE MEASUREMENTS AND PROPERTIES

To assess the “strength” of the particular granulating substance, it is possible to test the breaking strength of films made from it. Table 21.1 illustrates this for a series of traditional binders.

The table illustrates that the breaking strength is a function of moisture content. Gelatin bridges break more readily at higher moisture contents.

Table 21.1 Breaking Strength of Various Binders

Binder	Moisture in film (%)	Breaking strength (J/cm ²)
Gum arabic	9.8	1.4
Gelatin	10.8	12
	13.5	7.2
Methylhydroxyethyl cellulose	3.1	3.4
PVP (povidone)	10.4	1.0
Starch	8.1	18

Source: Healey et al., 1974.

Malamataris and Kortis (1997) studied granulations of lactose (subscript S in the following) and sulfadiazine (subscript L in the following) and employed a specially built rheometer to measure viscosity of the masses studied. They measured wettability parameters; namely, the contact angle θ between granulating liquid and powder, the surface tension of the liquids used, γ representing either γ_L or γ_S , and the work of adhesion, W_a which is given by

$$W_a = \gamma\{1 + \cos[\theta]\} \tag{21.1}$$

and the spreading coefficients, λ_{LS} given by

$$\lambda = W_a - 2\gamma \tag{21.2}$$

Granule “strength” may be tested in different manners (e.g., by the method published by Harwood and Pilpel, 1968). Malamataris and Kortis (1997) tested the tensile strength of the granulations as a function of water consumption by methods published by Ashton et al. (1964) and Eaves and Jones (1972). Samples of granulation were placed in a cell, and a consolidating stress applied. The tensile strength at the particular packing fraction was obtained from the weight, the cross-section, and the force required to sever it. Profiles constructed from their data are shown in Fig. 21.4.

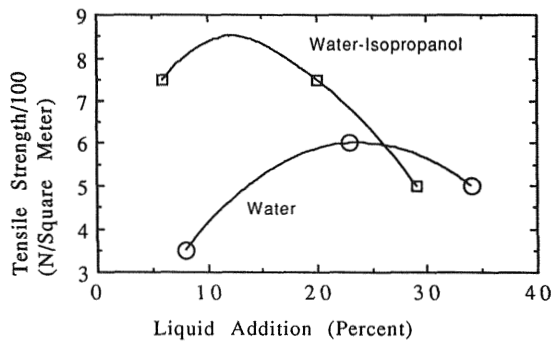


Fig. 21.4 Tensile strength of granulation as a function of water consumption. (Data from Malamataris and Kortis, 1997.)

The tensile strength of granules increase with increasing drying temperature (Capes, 1984). The strength is a function of the “liquid saturation” (i.e., the percentage of void space in the wet granules that is occupied by granulation liquid). It has been shown, experimentally (Capes, 1984), that when the crust is removed the granule attains its maximum tensile strength at about 20% liquid saturation. However, in the processing of granulations with soluble fillers (e.g., lactose), the liquid saturation is a function of granulation time, because the longer the granulation goes on, the more lactose will be dissolved. This is a point that is of importance in “granulation endpoints,” to be discussed shortly.

Granule strength is also an (almost linear) function of granule size (Gold et al., 1971), and it increases exponentially with the amount of binder content in the dry granules (Strickland et al., 1956). The work exerted in crushing granules, in general, increases with moisture content (Ganderton and Hunter, 1971).

21.4. PHYSICS OF THE PROCESS

When powder is placed in a mixer and blender, there is a certain, but not substantial, resistance by the powder mass to the process. The forces that must be overcome are van der Waals and frictional. As granulating liquid (or simply water) is added, this resistance increases, and the resistance is largely independent of the mixer (Malamataris and Kortis, 1997; Hunter and Ganderton, 1973; Bier et al., 1979; Lindberg et al., 1982; Ritala et al., 1988; Wan and Prasad, 1988; Usteri and Leuenberger, 1989; Ritala and Virtanen, 1991). It is the mass itself that causes the torque on the blades.

21.5. GRANULATION ENDPOINTS

The mixer torque rheometer has been used to study wet granulations by a series of investigators (Rowe and Sadeghnejad, 1987; Parker et al., 1990a, 1991, 1992; Hancock et al., 1991, 1992; Landin et al., 1995). Chatlapalali and Rohera (1998) have described torque versus time curves of diltiazem HCl-cellulose wet granulations, using hydroxypropyl methylcellulose, hydroxyethyl cellulose, and microcrystalline cellulose as excipients. Hydroxypropyl cellulose was used as binder, and granulations were carried out with isopropanol. In all cases there were wetting, poor liquid spreading, and weak interaction between substrate and binder. The hydroxypropyl methylcellulose system was capable of extrusion-spheronizing. The critical liquid percentage depended on the system in question.

Although proposed earlier, Bier et al. (1979) originated the first systematic study of power consumption measurements in a granulation kneader to establish a granulation endpoint. A typical curve is shown in Fig. 21.5. Ritala et al. (1988) and Ritala and Virtanen (1991), Usteri and Leuenberger (1989), Lindberger et al. (1982), and Wan and Prasad (1988) have also described the instrumentation of torque during the granulation process.

The time of kneading is also important, especially when soluble excipients (either drug or filler) are used. Because lactose is often used, and its solubility is 1 g in 2.5 mL of water, substantial amounts of lactose may go into solution if the process is allowed to go on for too long (see Figs. 21.1 and 21.3). *In other words, granulation is, most often, not an equilibrium process, and must be halted before reach-*

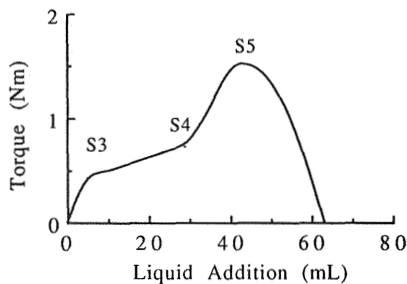


Fig. 21.5 Typical torque versus liquid addition curve for a granulation process.

ing an equilibrium situation. For many years, the granulation endpoint was empirical, and it was determined by the operator. In recent years, monitoring of the torque on the mixing motor (or placing load cells on the mixing vessel), will allow signals that change as a function of kneading time.

What happens in general is that the initial addition of liquid is too localized, so that kneading first allows distribution of the water. After a certain time an “equilibrium granule” (which truly is not an “infinite time granule” will occur (Carstensen et al., 1976a,b).

21.6. GRANULE DENSITY AND POROSITY

In granules, the properties of density and porosity are interrelated; hence, they will be treated compositely.

A schematic representation of pores in a granule is shown in Fig. 21.6. Pore size distributions may be deduced from hysteresis loops in adsorption isotherms. The capillary pressure, P , of a liquid with interfacial tension γ and contact angle $[\theta]$ in a capillary of radius r is

$$P = 2\pi r \gamma \cos[\theta] / (2\pi r^2) = 2\gamma \cos[\theta] / r \quad (21.3)$$

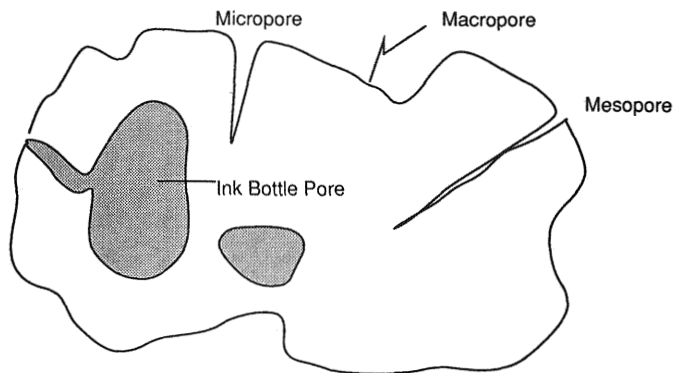


Fig. 21.6 Schematic representation of pores in a granule.

where γ is the interfacial tension between adsorbate and substrate, and θ is the contact angle. If such a liquid is condensed into a capillary pore with radius r then the Kelvin equation states that

$$\ln[P/P_0] = -2\gamma V/rRT \quad (21.4)$$

where P is the vapor pressure of the adsorbate over the pore, V is its molar volume, R is the gas constant, T is absolute temperature, and P_0 is the bulk vapor pressure of the adsorbate.

The total porosity ε (regardless of distribution) can be calculated, if the true, crystallographic density of the solid ρ is known, by measuring the apparent density ρ' of the particle, by a previously stated formula:

$$\varepsilon = 1 - (\rho'/\rho) \quad (21.5)$$

Pores with diameter above $8\text{ }\mu\text{m}$ are referred to as megapores (and the upper radius for those is usually in the range of $20\text{--}40\text{ }\mu\text{m}$). Above this upper limit the pore is essentially part of the surface rugosity. Pores with radii of $0.04\text{--}8\text{ }\mu\text{m}$ are denoted micropores, and pores smaller than $0.04\text{ }\mu\text{m}$ are mesopores.

Mercury intrusion porosimetry is usually used for measuring *pore size distributions*. This is applicable to pure solids as well as to granulations (Fig. 21.7).

The surface area can be calculated from the pore distribution by graphically integrating the penetration volume against the intrusion pressure. The reason for this is the following: First, assume that the pores are cylinders (the so-called bunch of cylinders model). If a length h of cylinder is long compared with its radius r , then its volume V relates to its area A by

$$V/A = h\pi r^2/\pi 2rh = r/2 \quad (21.6)$$

The term PV now becomes

$$PV = PA r/2 \quad (21.7)$$

Since

$$P = -2\gamma\rho\cos[\theta]/r \quad (21.8)$$

this, inserted in Eq. (21.7) gives

$$PV = -\gamma\rho A\cos[\theta] \quad (21.9)$$

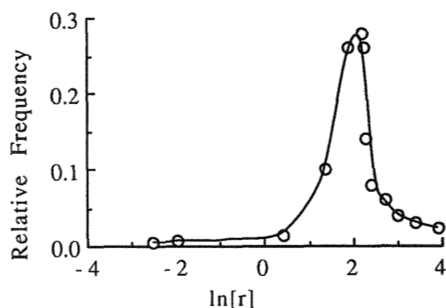


Fig. 21.7 Approximate pore size distribution of microcrystalline cellulose (Avicel). (Data from Marshall and Sixsmith, 1974/75.)

or

$$P_r dV_r = \gamma \rho \cos[\theta] dA \quad (21.10)$$

or, integrated from r_1 to r_2

$$\text{Area under } PV \text{ diagram} = \gamma \rho \cos[\theta] A \quad (21.11)$$

The relation may be deduced directly as well, for *any type of pore shape*, in that the work required to create an area of dA is

$$PdV = -\gamma \rho \cos[\theta] dA \quad (21.12)$$

and integration of this, directly, leads to Eq. (21.11). For microcrystalline cellulose this gives values of the order of $1.0 \text{ m}^2/\text{g}$.

Helium pycnometry (or wet pycnometry at times) can be used to determine the density of granules ρ_g which includes inkbottle pores and pore space with pore radius of less than $8 \mu\text{m}$. Mercury porosimetry can be used to determine the distribution of pore sizes within a granule. In the latter, the evacuated solid is exposed to a surrounding of mercury and a pressure P is applied. Denoting by γ , the interfacial tension between mercury and the solid (usually 0.48 N/m), and by θ the contact angle (usually $135\text{--}140^\circ$) of mercury with the solid, then the Washburn equation (Lowell and Shields, 1991) applies (here repeated for convenience):

$$P = -2\gamma \cos[\theta]/r \quad (21.13)$$

The mercury porosimeter measures the total volume V intruded at pressure, and this volume represents the pore volume, with radii larger than the value of r calculated from Eq. (21.13).

The *bed* density ρ_b of populations of granules is, as discussed previously,

$$\rho_b = 1 - (\rho_d/\rho_g) \quad (21.14)$$

The particle density (i.e., the intragranular porosity) is also obtained by mercury intrusion porosimetry.

Vertommen et al. (1998) have determined the *granule density* of pellets made by spheronization (to be covered in the following), and found the granule density to include the pores that are closed (inkbottle pores) and open pores that have a radius less than $8 \mu\text{m}$. This is along the same lines as the findings of Carstensen and Hou (1985).

Granule hardness has been measured by Harwood and Pilpel (1968) and by Mehta et al. (1978). In the latter case, dried granules of a certain mesh cut were placed in a ball mill, which was rotated for different lengths of time. The rate at which fines were produced is approximately first-order, in the sense that the amount left on the original retaining screen size decreases loglinearly in time. The rate constant obtained from this is an index of the granule hardness.

Granule friability is often measured, as well. Baba and Sugimoto (1965) and Marsh (1961) have described methods for measuring this characteristic.

21.7. EXTRAGRANULAR POROSITY

In high-speed machines, the extragranular porosity (or the dependent bulk density) is of importance, because to obtain a certain amount of powder in a tablet die, there is a certain (machine adjusted) volume between the die table and the lower punch at weight position. This may vary from batch to batch, but the larger this volume is, the longer the stroke of the punches will be. Furthermore, the powder consolidates in the die as the punches come down on it, and the speed of the punch, in general, is greater than that of the consolidation rate, so that the number of bonds that are created would be the larger, the lower the porosity. These are subjects that will be discussed in Chap. 23.

It is obvious from previous chapters, that the packing of a powder (i.e., its bed or extragranular porosity) is a function of the shape factors (e.g., of the *shape coefficient*, α_S/α_ω). The work by Ridgway and Rupp (1969) and Pitkin and Carstensen (1990) has been quoted previously, and one of their findings was that the bulk density decreases linearly with increase in the shape coefficient.

In line with the statements on the die fill, Fair and Hatch (1933) showed that the coefficient of variation of a die fill increased linearly with the shape coefficient (i.e., the more “irregular” a granule shape, the higher the weight variation might be expected in a tableting operation). This fact may be more applicable to direct compression (where there is no significant operational control of particle shape) than to wet granulates, because one of the intents of wet granulation is, indeed, to make the particle “round.”

The extragranular porosity is affected by the rate of addition of the granulation liquid (Fig. 21.8). The raw data for this graph are taken from the publication by Davis and Gloor (1971). Their data show that the porosity approaches a limiting

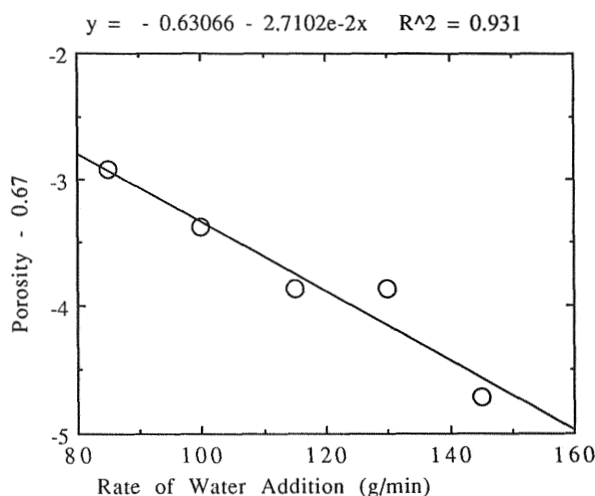


Fig. 21.8 Effect of rate of water addition on the extragranular porosity of a wet granulation. The porosity approaches a limiting value of 0.67 and the logarithm of the porosity minus this figure is plotted versus rate of addition. (Data from Davis and Gloor, 1971.)

value of 0.67, and in the presentation here the logarithm of the porosity minus this figure is plotted versus rate of addition.

Often, manufacturing batch sheets do not include addition rates, and as seen this parameter has an effect on the extragranular porosity. "External" water, at times, acts as a lubricant; hence, the more the lubricant (Neuman, 1967) the more readily the powder will attain a closer configuration.

The temperature of drying is also of importance, as seen in Fig. 21.9. It is obvious that the porosity will approach a limiting value (in the figure, 0.75), and that temperatures above 70°C are usually not used.

It may be assumed (as shown by Zoglio et al., 1976, 1980) that the moisture in a "dried" granule is not, necessarily evenly distributed (Pitkin and Carstensen, 1973), but that there is less on the surface than in the core, unless the granule is very small.

Because the surface moisture is a sort of lubricant, there will be a closer packing with more surface moisture (the lower the drying temperature) and this in turn will give a smaller extragranular porosity, in line with the trend shown in Fig. 21.9.

This is also demonstrated by the work of Armstrong and March (1976), and this is shown in Fig. 21.10. There is less sensitivity to moisture content, the larger the diameter of the particle, because there is less "surface moisture" in the larger granules, other factors being equal (Fig. 21.10 simply gives gross, overall moisture content of the granule). That the specific surface area of the larger granule is smaller is the important factor. The frictional coefficient would be a function of surface moisture and the total friction would be proportional to this and inversely proportional to the area. Hence, the smaller moisture dependency at higher diameters.

The curves in Fig. 21.10 are fairly well described by parabolas, and a parameter describing their "flatness" would be the coefficient to x^2 . If these coefficients are plotted versus diameter, then a linear plot ensues (Fig. 21.11).

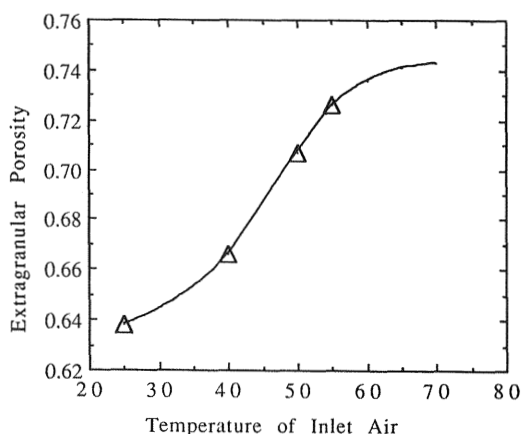


Fig. 21.9 Effect of temperature on extragranular porosity. (Data from Davis and Gloor, 1971.)

$$y = 0.35029 + 1.4914e-2x - 3.1429e-4x^2 \quad R^2 = 0.915$$
$$y = 0.26371 + 1.3314e-2x - 2.2857e-4x^2 \quad R^2 = 0.956$$
$$y = 0.42266 + 1.5781e-3x - 3.9028e-5x^2 \quad R^2 = 0.941$$

○ d(avg) = 26 micron

□ d(avg) = 70 micron

△ d(avg) = 140 micron

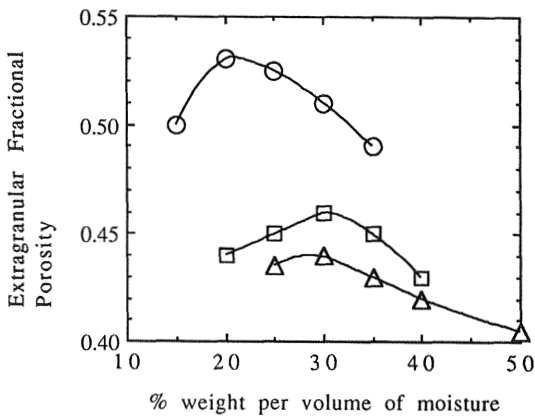


Fig. 21.10 Extragranular porosity as a function of moisture content of granules. (Data from Armstrong and March, 1976.)

21.8. USE OF FLUID BED GRANULATION

It is not the purpose in this text to delve on the intricacies of fluid bed drying. The principle, however, is briefly schematized in Fig. 21.12. The powder to be granulated is transferred to a basket with a mesh bottom. This is placed in the fluid bed dryer in such a fashion that air can be let in at the bottom of it, and the air velocity is then adjusted so that the particles become “airborne” (i.e., fluidized). The air velocities must be kept between the *incipient fluidization velocity* (i.e., the velocity that just

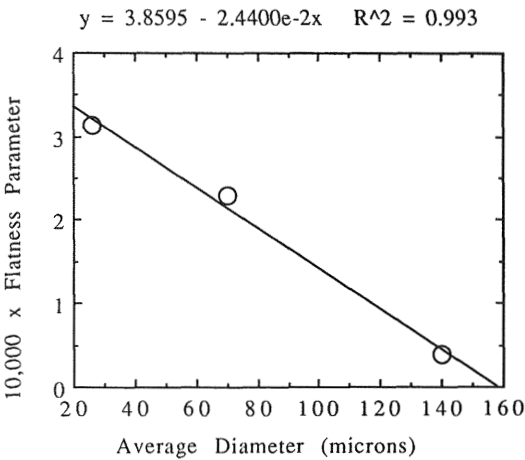


Fig. 21.11 Flatness of distribution as a function of particle diameter. (Data from Armstrong and March, 1976.)

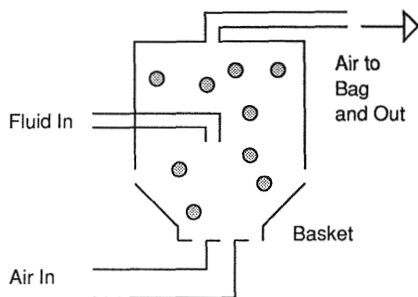


Fig. 21.12 Schematic of fluid bed granulator.

fluidized the powder), and the *entrainment velocity* (i.e., the velocity that would simply carry the powder out the exit tube).

Granulation liquid is then pumped into and sprayed onto the granulation. Drops attach themselves to the powder and agglomerate it, and the airstream dries it. A delicate balance between spraying rate and air velocity and temperature must be maintained. If the spraying rate is too fast, then the mass will simply wet down, and if it is too slow, then the droplets may dry before reaching the solid particles.

The inlet fluid may be either a binder solution or water. In the latter, a granulating agent (PVP or pregelatinized starch) will be part of the powder and will act as a binding agent when the water is added.

Sunada et al. (1999) have shown that fluidized bed granulation, in comparison with agitation granulation, gives rise to granules that have greater plastic deformability and less granule hardness. The granules are compact, and with 70% drug (ethenzamide) have longer dissolution and disintegration times. The binders used by these authors were (a) lactose–cornstarch and (b) HPC.

The manner in which a wet binder is incorporated into the massing is a most important factor. Arnaud et al. (1998) studied nitrofurantoin (20%) granulations with 38% lactose and 37% cornstarch and compared four granulation procedures: (a) wet granulation in a Lödige mixer, (b) granulation in a fluid bed granulator (Glatt), (c) dry granulation, and (d) roller compaction. Wet-granulated granules were harder than those made by dry process. The mixer granulations were harder than the fluid bed granulations.

The particle size distributions from fluid–bed–granulated material are mostly lognormal, and this is demonstrated in the following manner (Mehta et al., 1977).

The granulation process is assumed to produce n particles, where $1 < n < N$, where N is an upper limit. (For instance n must be smaller than, or equal to, the number of particles placed in the granulator.) The formation of the aggregates occurs by collision of either particles or aggregates with liquid, and there is a probability of this happening that is proportional to the number of particles or aggregates n present at time t ; that is,

$$dn/dt = bn \quad (21.15)$$

here, b is a constant that depends on the collision and detachment probabilities. The mass M , is proportional to n , so that

$$dM/dt = M/\phi \tag{21.16}$$

where the proportionality constant is expressed as $1/\phi$ for later notational convenience. Integration of Eq. (21.16) gives

$$t = h + \phi \ln[M/M_{\text{avg}}] \tag{21.17}$$

where M_{avg} is the average aggregate mass.

The time of growth t is different for each particular aggregate (Irani and Callis, 1968) and is normally distributed about the mean growth time, τ . A reduced time θ is now introduced:

$$\theta = t - h \tag{21.18}$$

Since t is distributed normally with a mean of τ , θ will be distributed normally with a mean of $t - \tau$.

$$\theta = \phi \ln[M/M_{\text{avg}}] \tag{21.19}$$

but, since θ is normally distributed it follows that $[M/M_{\text{avg}}]$ is normally distributed.

21.9. PELLETS

Although some stress is applied in ordinary wet granulation, this is relatively small compared with that exerted in pelletizing. There are several systems for pelletizing wet masses, the most common being the screw extruder, a schematic of which is shown in Fig. 21.13a.

This is akin to a meat grinder, and sufficient pressure is usually exerted so that some elastic and plastic deformation of the solid particles result. Air is, obviously, expelled, so that the wet strings (akin to spaghetti) are quite compact (nonporous).

Shaping is often accomplished in a balling disk (see Fig. 21.13b) and is often referred to as spheronization.

Pellets made by wet granulation followed by extrusion and spheronization have been described (Zimm et al., 1996; Johansson et al., 1968; Wan et al., 1994, 1995; Holm et al., 1996; Vertommen and Kinget, 1997, 1998). Zimm et al. used microcrystalline cellulose and (10%) acetaminophen for their composition.

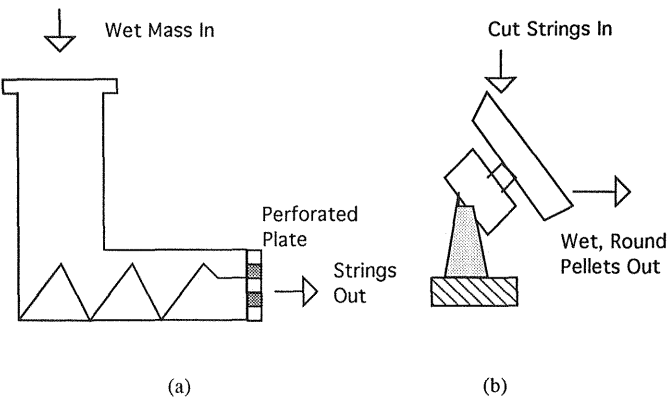


Fig. 21.13 (a) Screw extruder, (b) balling disk.

Agglomeration liquids may be, for instance (as exemplified by Johansson et al., 1998), ethanol/water 70:30, and the pelletization procedure may be spheronization or extrusion-spheronization.

Vertommen et al. (1998) have studied the structure of such products by determining the true density by helium pycnometry, the specific surface area (by gas adsorption), pore space (by mercury intrusion), and appearance by scanning electron microscopy.

The mercury intrusion established the presence of macropores ($0.05\text{--}7\text{ }\mu\text{m}$). Pores are closed as the spheronization processes, and air pockets form in the pellets. High rotor speed and long spheronization times will reduce the pore volume.

Zimm et al. (1996) compared dissolution rates from spherical pellets by two release models described in the following. The nomenclature used is:

a = the radius of the pellet not extracted

a_0 = the radius of the pellet

Q = mass of drug released per square centimeter (cm^2) of pellet surface

D = diffusion coefficient

A_1 = grams of drug per cubic centimeter (cm^3) of pellet

S = solubility (g/cm^3)

t = time

ε = porosity (dimensionless)

τ = tortuosity

The two models compared were:

1. The Higuchi square-root model, which is given by

$$Q = [(D\varepsilon/\tau)(2A_1 - \varepsilon S)St]^{1/2} \quad (21.20)$$

2. The Higuchi cube equation given by

$$1 + (a/a_0)^{1/3} - 3(a/a_0)^2 = 6D\varepsilon St/(\tau A\alpha_0^2) \quad (21.21)$$

It was not possible, statistically, to distinguish between the two models, each giving high statistical probability of fit.

21.10. GRANULE SIZE DETERMINATION (SIEVE TEST)

The most common method for determining granule sizes are by means of sieve tests. Particle size distributions may be normal or lognormal (Steiner et al., 1974) when the granules are made in a kneader or, as mentioned earlier (Mehta et al., 1977), by fluid bed granulation.

The sieving of particulate pharmaceuticals has been reported (Fonner et al., 1966; Whitby, 1958; Carstensen, 1977). Usually, a given time for a sieve test is prescribed, and the weight obtained on the various screens is recorded. If the fraction in one particular sieve fraction (e.g., 30/40 mesh) is selected, and resieved, some of the material will pass through. Carstensen (1977) found that the percentage passing through the sieve was a linear function of the logarithm of sieving time. Davies (1990) found that the logarithm of the amount passing was linear in the logarithm of time at low time points (region no. 1), but that a transition occurred (to region no. 2) after which the loglinear relation referred to in the

foregoing occurred (Fig. 21.14). Equilibrium is considered to occur when the transition to region 2 occurs. Prescribed times for screening should be made in such a fashion that region 2 has been reached.

21.11. DISSOLUTION FROM WET-PROCESSED GRANULES

It is intuitively obvious that the “looser” the granule, the better the drug should dissolve from it. The methods by which dissolution occurs from granules in general is dealt with in the following.

The data reported by Arnaud et al. (1998) give rise to the dissolution profiles shown in Fig. 21.15 and show the comparative dissolution rates. The wet-granulated products gave better qualities in other respects.

The trend is actually the opposite of what most often is encountered, at least with hydrophobic drugs. In this case the wet granulation imparts hydrophilicity to the composition, which allows more rapid dissolution. One important aspect is the shape of the (two lower) curves. The manner in which a drug is released from a granule is the following: The contact angle is usually small (because the binder is hydrophilic), so there is no wetting lag time, and dissolution medium penetrates the pore space of the granule. The drug substance then forms a saturated solution of the liquid in the pore space, and the drug *diffuses* out into the bulk liquid.

By Fick's law

$$(1/A)dM/dt = -DdC/dx \quad (21.22)$$

where A is the external surface area of the granule, M is the mass inside the granule, t is time, C is concentration, x is distance, and D is the diffusion coefficient. The minus sign in Eq. (21.22) stems from the fact that the mass time gradient is of opposite sign from the concentration distance gradient. The concentration in the granule pore space is assumed to be the solubility, and this drops to the concentration in the bulk C_b over a distance of h (assuming there is a stagnant film of this thickness on the surface of the granule). Hence,

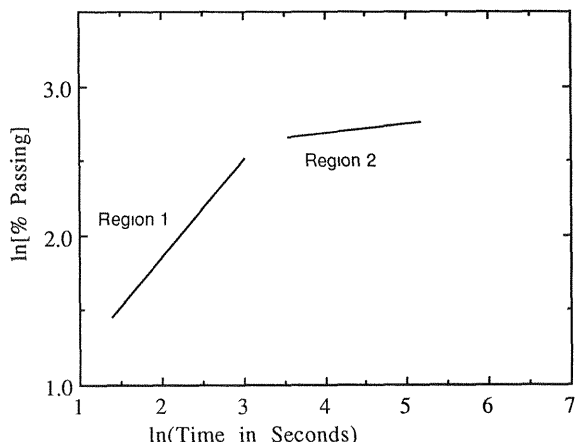


Fig. 21.14 The percentage of material passing a sieve as a function of sieving time. (Data from Davies, 1990.)

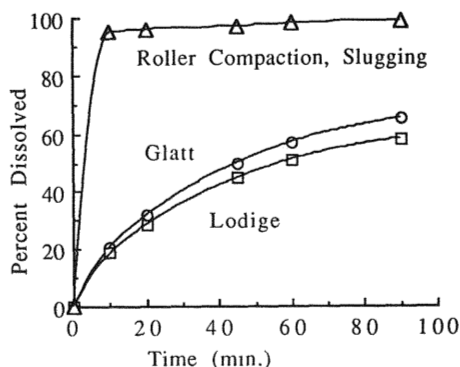


Fig. 21.15 Dissolution curves from differently processed nitrofurantoin granules. (Data from Arnaud et al., 1998.)

$$dC/dx = (S - C_b)/h \quad (21.23)$$

The amount undissolved at time t is M , so that amount dissolved is $M_0 - M$, where M_0 is the initial drug amount; that is, the concentration in the bulk liquid is

$$C_b = (M_0 - M)/V \quad (21.24)$$

where V is the volume of the dissolution liquid. It is noted that

$$-dM/dt = VdC/dt \quad (21.25)$$

Inserting Eqs. (21.24) and (21.25) into Eq. (21.22) now gives

$$VdC/dt = \{D/h\}(S - C_b) \quad (21.26)$$

which integrates to

$$\ln[S - C_b] = \{D/hV\}t + \ln\{S\} \quad (21.27)$$

where the initial condition that $C_b = 0$ $t = 0$ has been invoked. By adding $\ln[V]$ to both sides Eq. (21.28) results.

$$\ln[F_0 - F] = \{D/hV\}t + \ln\{F_0\} \quad (21.28)$$

where F is the amount (mass) of drug released and F_0 is the maximum amount dissolvable in the dissolution medium.

At times (as in the two lower curves in Fig. 21.9) some of the material has been “encased” in the granules to such an extent that it is no longer available. If this amount is denoted F_∞ , then Eq. (21.28) takes the form

$$\ln[F_\infty - F] = \{D/hV\}t + \ln\{F_\infty\} \quad (21.29)$$

where F_∞ can be obtained by iteration, or knowledge of S (which here would be smaller than F_0/V). If, in Fig. 21.15, the value of F_∞ had been 0.35 of the total amount, then one may have plotted the lower curve in Fig. 21.16 by plotting $\ln[0.45 - F]$ as a function of time, where F is fraction of drug released.

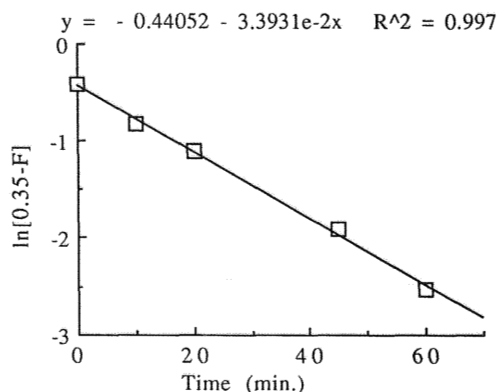


Fig. 21.16 Data from Fig. 21.9 plotted according to Eq. (21.29).

In general, no adjustment is necessary, and Eq. (21.28) applies directly. It is most often used in the form

$$\ln[M/M_0] = -K_g t \quad (21.30)$$

where K_g is the dissolution constant (in reciprocal time units).

21.12. SPHERONIZATION

When a wetted, solid mass is extruded, it appears in strings that are either cut or fall apart in cylindrical segments. These may be fed into a slanted plate and rotated in such a fashion that they become spherical.

Newton (1990) and Bains et al. (1991) have investigated the effect of process variables. Of these, the conditions of the feeding screw in the extruder, the revolutions per minute (rpm) of the spheronizer, the spheronizing time, the wet mix time, and the water content are the principal variables. Hileman et al. (1997) studied these, and a graph based on their data is shown in Fig. 21.17.

The porosity of extruded, spheronized granules is much lower than that of granules made by conventional means.

SYMBOLS

A = surface area

A_1 = g of drug/cm³ of pellet

a = the radius of the pellet not extracted

a_0 = the radius of the pellet

C = concentration

C_b = concentration in bulk solution

D = diffusion coefficient

h = thickness of stagnant layer

k = intrinsic dissolution rate constant (cm/s)

K_g = granule dissolution constant (min⁻¹)

M_0 = initial amount of drug

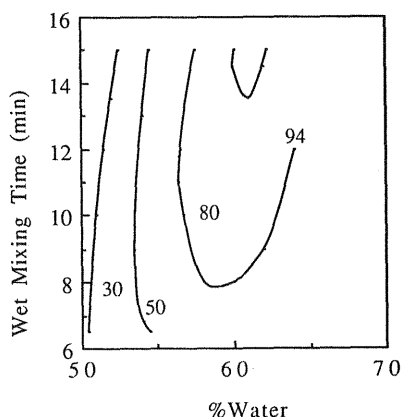


Fig. 21.17 Yield of 20-mesh pellets after a spheronizing time of 12 min as a function of mixing time and water content. Active drug: theophylline with an nonionic binder. (From Hileman et al., 1997.)

M = amount of drug retained in the dosage form

P = (a) vapor pressure of adsorbate over a pore; or (b) intrusion pressure

P_0 = bulk vapor pressure of the adsorbate

Q = mass of drug released per square centimeter (cm^2) of pellet surface

F = amount of drug released into the dissolution medium

F_∞ = amount of drug released at infinite time

R = the gas constant

r = pore radius

S = solubility

t = time

T = absolute temperature

V = molar volume

W_a = work of adhesion

α_S/α_V = shape coefficient

γ = interfacial tension between adsorbate and substrate

ϕ = contact angle

ε = porosity

λ_{LS} , or λ = spreading coefficient

ρ = true, crystallographic density of the solid

ρ' = apparent density

ρ_b = bed density

ρ_g = granule density

τ = tortuosity

RECOMMENDED READING

Fonner DA, Anderson NR, Banker GS (1981). In: Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms*, vol. 2. Marcel Dekker, New York, pp 185–261.

Gordon RE, Rosanske TW, Fonner DE (1990). In: Lieberman HA, Lachman L, eds. *Pharmaceutical Dosage Forms*, vol. 2. Marcel Dekker, New York, pp 245–300.

REFERENCES

- Arnaud P, Brossard D, Chaumeil JC (1998). *Drug Dev Ind Pharm* 24:57.
- Baba M, Sugimoto K (1965). *Annu Rep Shionogi Res Lab* 15:227.
- Bains D, Boutell LS, Newton JM (1991). *Int J Pharm* 69:233.
- Bier HP, Leuenberger H, Sucker H (1979). *Pharm Ind* 41:375.
- Capes (1984). In: Fayed ME, Otten L, eds. *Handbook of Powder Science and Technology*. Van Norstrand Reinhold, New York, p 41.
- Carstensen JT, Hou X-P (1985). *Powder Technol* 42:153.
- Carstensen JT, Lai T, Flickner DW, Huber HE, Zoglio MA (1976). *J Pharm Sci* 65:992.
- Chatlapalali R, Rohera BD (1998). *Int J Pharm* 161:179.
- Chowhan ZT (1980). *J Pharm Sci* 69:1.
- Chowhan ZT, Palagyi L (1978). *J Pharm Sci* 67:1335.
- Chowhan ZT, Chow YP (1981). *J Pharm Sci* 70: 1134.
- Davies (1990). In: Fayed ME, Otten L, eds. *Handbook of Powder Science and Technology*. Van Norstrand Reinhold, New York, p 41.
- Fair GM, Hatch LP (1933). *J Am Water Works Assoc* 25:1551.
- Fonner DE, Banker GS, Swarbrick J (1966). *J Pharm Sci* 55:576.
- Gudsoorkar, Khanna S (1980). *Indian Drugs Pharm Ind*.
- Hancock BC, York P, Rowe RC, Parker MD (1991). *Int J Pharm* 76:239.
- Hancock BC, York P, Rowe RC (1992). *Int J Pharm* 83:147.
- Harwood CF, Pilpel N (1968). *J Pharm Sci* 57:478.
- Healey JNC, Rubinstein MH, Walters V (1974). *J Pharm Pharmacol* 26:41P.
- Hileman GA, Upadrashta SM, Neau SH (1997). *Pharm Dev Technol* 2(1):43.
- Holm P, Bonde M, Wigmore T (1996). *Pharm Technol Eur* 8:22.
- Hou X-P, Carstensen JT (1985). *Int J Pharm* 25:207.
- Hunter BM, Ganderton D (1973). *J Pharm Pharmacol* 25S:71P.
- Johansson B, Nicklasson F, Alderborn G (1998). *Int J Pharm* 163:35.
- Krycer I, Pope DG, Hersey JA (1983). *Powder Technol* 34:39.
- Landin M, Row RC, York P (1995). *J Pharm Sci* 84:557.
- Lindberg NO, Leander L, Reenstjerna B (1982). *Int J Pharm* 8:775.
- Lowell S, Shields JE, eds. (1991). *Powder Surface Area and Porosity*, 3rd ed. Chapman & Hall, London.
- Malamataris S, Kiortis S (1997). *Int J Pharm* 154:9.
- Marsh DM (1961). *J Sci Instrum* 38:229.
- Marshall K, Sixsmith D (1974/1975). *Drug Dev Ind Pharm* 1:51.
- Mehta A, Zoglio MA, Carstensen JT (1978). *J Pharm Sci* 67:905.
- Nagay A, Keresztes K, Pitye-Hódy, Selmech B, Kedvessy G (1980). *Bull Pharm Technol Inst Univ Szeged [Szeged, Hungary]* 35:168.
- Neumann BS (1967). *Adv Pharm Sci* 2:181.
- Newitt DM, Conway JM (1958). *Trans Inst Chem Eng* 36:422.
- Newton JM (1990). *STP Pharma* 6:396.
- Parker MD, York P, Rowe RC (1990). *Int J Pharm* 64:207.
- Parker MD, York P, Rowe RC (1991). *Int J Pharm* 72:243.
- Parker MD, York P, Rowe RC (1992). *Int J Pharm* 80:179.
- Pitkin C, Carstensen JT (1973). *J Pharm Sci* 62:1215.
- Pitken C, Carstensen JT (1990). *Drug Dev Ind Pharm* 16:1.
- Rak J, Chalabala M (1975). *Pharm Univ Comenianae* 28:35 [Bratislava].
- Ridgway K, Rupp R (1969). *J Pharm Pharmacol* 21:30S.
- Ritala M, Virtanen S (1991). *Acta Pharm Nord* 3:229.
- Ritala M, Holm P, Schaefer T, Kristensen HG (1988). *Drug Dev Ind Pharm* 14:1041.
- Rowe RC, Sadeghnejad GR (1987). *Int J Pharm* 38:229.

- Shotton E, Edwards NJ (1974). *J Pharm Pharmacol* 26:107P.
- Steiner G, Patel MR, Carstensen JT (1974). *J Pharm Sci* 63:1395.
- Sunada H, Hasegawa M, Tadashi M, Sakamoto H, Fujita K, Tanino T, Kokubo H, Kawaguchi T (1998). *Drug Dev Ind Pharm* 24:225.
- Usteri M, Leuenberger H (1989). *Acta Pharm Technol* 35:163.
- Vertommen J, Rombaut P, Kinget R (1997). *Drug Dev Ind Pharm* 23:39.
- Vertommen J, Rombaut P, Kinget R (1998). *Int J Pharm* 161:225.
- Wan LSC, Prasad KPP (1988). *Acta Pharm Technol* 35:163.
- Wan LSC, Heng PWS, Liew CV (1994). *Drug Dev Ind Pharm* 20:2551.
- Wan LSC, Heng PWS, Liew CV (1994). *Ind J Pharm* 118:213.
- Whitby KT (1958). *ASTM Spec Tech Publ* 235.
- Zimm KR, Schwartz JB, O'Connor RE (1996). *Pharm Dev Technol* 1:37.
- Zoglio MA, Carstensen JT (1983). *Drug Dev Ind Pharm* 9:1417.
- Zoglio M, Huber HE, Koehne G, Chan PL, Carstensen JT (1976). *J Pharm Sci* 65:1205.

This Page Intentionally Left Blank

Hard-Shell Capsules

22.1. The Two-Ring Hard-Shell-Filling Machine	376
22.2. Other Filling Principles than the Two-Ring Machine	379
22.3. Principles of Fills and Volumes	380
22.4. Compaction During Hard-Shell Filling	381
22.5. Dissolution and Disintegration of Hard-Shell Capsules	382
22.6. Pelliculation	383
22.7. Sustained-Release Hard-Shell Capsules	384
Symbols	385
References	385
Recommended Reading	386

Hard-shell capsules are a dosage form that is resorted to when a drug substance is poorly compressible in the desired dosage strength and is moisture-sensitive. It also, at times, results from decisions early in product development, during which original clinical trials were performed in capsules, because of convenience, and the trials went ahead too rapidly to economically change the dosage form. The time lapse between conception of a drug and its introduction into the market place is of importance, and even though hard-shell capsules may be more expensive and cause other problems not encountered in other solid-dosage forms, the development of the dosage form is easier and, in some aspects, more foolproof than direct compression- or wet granulation-based tablets (if those are possible with the drug substance). An example of a drug substance that was introduced into the market place as a capsule because the development got too far ahead of itself is chlorthalidone HCl (Librium Hydrochloride) capsules. Four years later, when the tablet, Libritabs, was introduced, the public was used to a capsule, and the tablets were never a success.

22.1. THE TWO-RING HARD-SHELL-FILLING MACHINE

The commonly used hard-shell capsules are made of gelatin, formed into shapes that allow filling them with particulate matter. The mostly used shapes and sizes are shown in Fig. 22.1.

Before discussing the required powder requirements for hard-shell operations, it is useful, first, to *sketchily* describe the basic principles of the original hard-shell machine. Although it is not used much in actual production today, it is frequently used in early product development (e.g., phase I clinical batches). It is a convenient method for making small batches. For larger batches it is too slow and labor-intensive to retain the popularity it once had.

Figure 22.2 shows the basic principle on which the capsule separation operation is based. The basics of the machine is a set of two rings that fit together, and that have holes which in the upper ring correspond in diameter to that of the top of the capsule, and in the lower ring correspond in diameter to that of the body of the capsule (see Fig. 22.2a and b). Capsules, placed in a hopper, are fed down a so-called raceway with a rectifier bar that aligns the capsules so that they feed into the rings in the position shown in Fig. 22.2c. Vacuum is applied, and the two rings are separated (see Fig. 22.2d), so that all the bodies are now in the bottom ring, and all the tops are in the top ring.

The bottom ring is now transferred to a filling station (Fig. 22.3) where a movable hopper, containing the powder to be filled, is drawn over the ring, and powder fills into the body capsules. After one rotation the hopper is drawn back. The once empty bodies of the capsules are now filled with powder.

The ring with the now-filled bodies of the capsules is placed together with the top ring with the empty tops, and aligned so that the holes line up, they are placed against a plate (Fig. 22.4a). A peg-board is placed in alignment with them (see Fig. 22.4a) and then pushed in (see Fig. 22.4b) so that the bodies are forced into the tops, and the support plate is then removed (see Fig. 22.4c), the peg-board pushes all the way into the rings, so that the capsules can be ejected.

The rings may have one, two, or three circles of holes. One is shown in Fig. 22.4, and two are shown in Fig. 22.5. The hopper has an auger (see Fig. 22.5) which

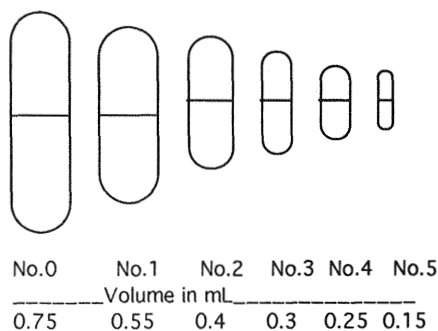


Fig. 22.1 Common shapes and sizes of hard-shell capsules. The volumes may depend on empty shell manufacturer, and other sizes have been reported in the literature: namely, 0: 0.68; 1: 0.50; 2: 0.37; 3: 0.30; 4: 0.21; 5: 0.13 mL.

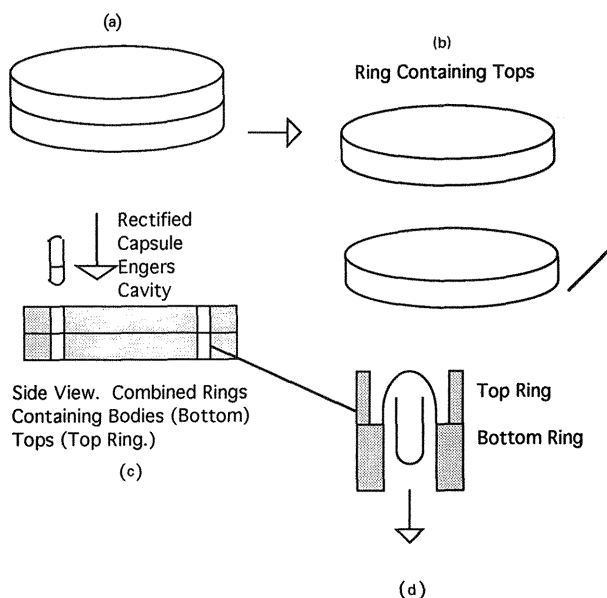


Fig. 22.2 Principle of a two-ring hard-shell machine.

may, or may not, be engaged. If it is engaged, then it helps push powder into the shells, if it is not engaged, then powder fills in simply by gravity.

In the former case, there is a forced consolidation of the powder, in the latter, there is none. The latter procedure is often used when sustained-release beadlets are filled, because the auger might crush the sustaining film. For this, as shall be discussed shortly, there is no internal pressure on the capsule, and to avoid separation of the halves in shipping, the capsules may be banded. By this procedure, a thin gelatin film is placed around the separation line between the halves and, aside from holding the halves together, this also tamper-proofs the product.

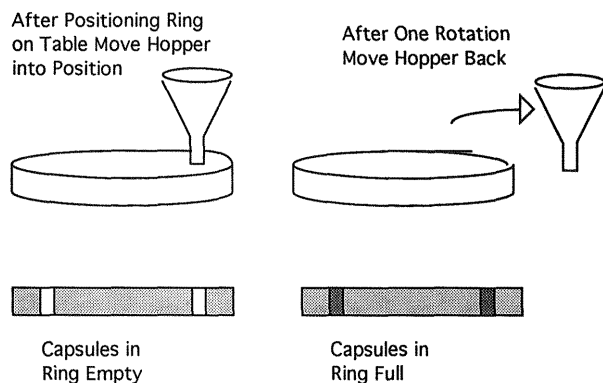


Fig. 22.3 Principle of filling the empty capsules in the bottom ring.

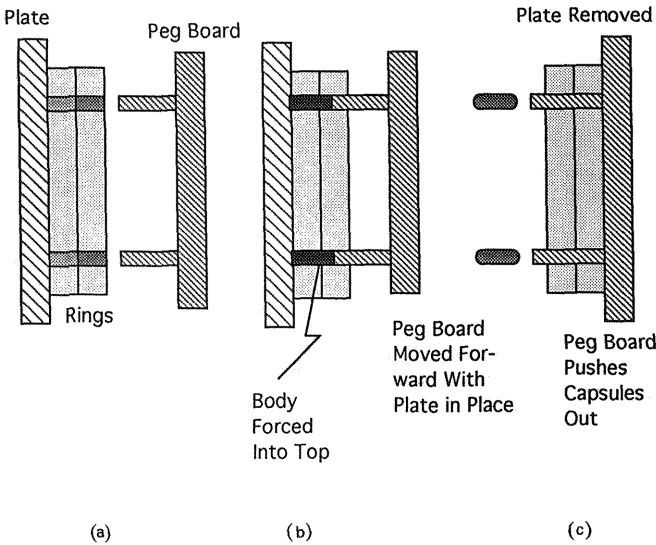


Fig. 22.4 Principle of ejection of capsules in a two-ring machine.

There will be an effect of flow rate both in free-flow fill, and in auger-forced fill. The “dwell time” τ (i.e., the length of time the body in the lower ring is in contact with the powder in the hopper) is the longer the length a of the hopper throat, and the shorter the rotational speed Ω rotations per second (rps), of the die table. If the flow rate, forced or not, is W g/s, then in τ s, $W\tau$ grams will flow into the capsule. The dwell time τ is given by the fact that the linear speed v of the hole under the hopper is

$$v = \Omega \, 2\pi R \tag{22.1}$$

so that the contact time is

$$\tau = a/(\Omega \, 2\pi R) \tag{22.2}$$

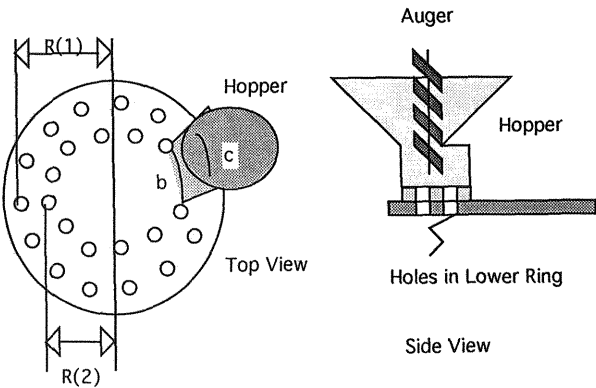


Fig. 22.5 Filling process on a two-ring machine.

where R is the radius of the circle of rings. If the fill dose is D g, then the amount that flows into the die must be D or more, that is, in the limit

$$D = W\tau = Wa/(\Omega 2\pi R) \quad (22.3)$$

For more than one row, the distance a differs from inner to middle to outer row (for three rows of rings) and from inner to outer row [for two rows of rings, i.e., R differs, $R(1)$ being larger than $R(2)$ in Fig. 22.5]. This is compensated by the protrusion on the hopper, making the distance b in Fig. 22.5 different from the distance c . Much of the fill weight variation experienced with multiple-ring filling is due to the different speeds of the hole circles, giving different contact times, in spite of the b and c features of the hopper construction.

From the foregoing, the minimum flow rate, forced or not as the situation may be, would be

$$W = D(\Omega 2\pi R)/a \quad (22.4)$$

Note that D is a function of Ω . The machine can be run at different speeds, so that the fill weight can be adjusted by way of adjustment of the rps.

22.2. OTHER FILLING PRINCIPLES THAN THE TWO-RING MACHINE

High-speed-filling machines usually depend on a dosator principle, which is outlined in Fig. 22.6.

The dosator is set at a given level, to assure a certain free volume. The filling principle is then that the powder is stomped into the dosator by the downward movement of it. (In some machines vacuum is employed in the void section to obtain the fill.) The dosator is then moved out of the bed.

The empty capsules are separated and the body of the capsule is made to coincide with the dosator, and downward movement of the pin, or simply gravity (or application of compressed air), ejects the powder. For precision this should have the nature of a plug.

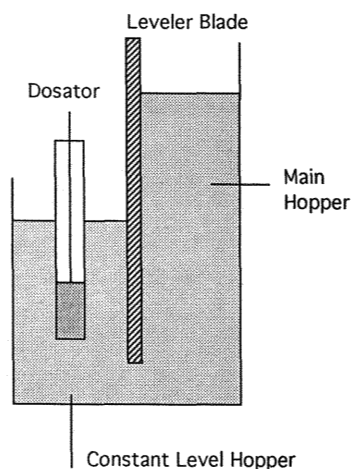


Fig. 22.6 Dosator principle.

The amount filled into the cavity of the dosator (hence, the fill weight) is a function of the apparent density, the compressibility (and indirectly of the particle size distribution).

Flow rate of the powder is important, because (see Fig. 22.6) the powder must flow in a controlled fashion from the main hopper into the constant level hopper. Control of this is accomplished, within limits, by the leveler blade.

It is obvious that the powder must be, to some degree, cohesive because a type of plug has to form. On the other hand it cannot be too cohesive, for flow then is impaired, making a constant level of powder difficult to achieve. The constant level is important, because the stroke of the dosator, and the amount of powder it encounters governs both the fill weight and the precision of fill.

After the body is filled, it is made to coincide with the top, and an insertion mechanism causes joining of top and body.

There are several brands of high-speed hard-shell capsule-filling machines, Häffliger Karg (HK) machine, the Zanazi, and the mG2 being the most common.

The HK machine has a storage hopper for empty capsules, a rectifier, a bulk powder hopper (as shown in the foregoing), a capsule-transport portion, a closing station, and an ejection station. The number after HK machines signifies the number of capsules that can be handled per minute with optimum operation (e.g., HK Model GKF 2500 will handle 2500 capsules per minute).

The mG2 is a continuous-motion machine, the model G38 operating at 1000 capsules per minute. It consists of (a) a hopper for empty capsules with rectifier, (b) a removal station for the capsule top, (c) a cleaning station, (d) a dosator, (e) a powder hopper, (f) a top holder station, and (g) a closing and ejection station.

The highest output of the Zanazi machines is 150,000/h. The BZ-72 model handles powders, pellets, and tablets. Some models have presorters for empty capsules, recovery system for powder, a sampling station for filled capsule, and a check-weigher system.

22.3. PRINCIPLES OF FILLS AND VOLUMES

To make hard shell capsule products, it is a *mixture* of drug substance and excipient (e.g. lactose and magnesium stearate) that is filled into the body of a hard-shell capsule of a known volume. The principle of manufacturing the dosage form is, as described earlier, to (a) separate the cap and body, (b) “fill” the body, and (c) bring the cap and body section together again. This principle applies to other capsule-filling machinery as well.

To obtain the correct fill in a capsule-dosage form requiring, for example, X mg of drug, the drug substance is mixed with Y mg of excipients. Y is selected so that the mixture has the “correct” volume.

If the *appropriate* apparent density is ρ' , and the volume of the capsule is V , then

$$V = (X + Y)/\rho' \quad (22.5)$$

from which Y can be calculated. The problem, however, lies in the term *appropriate*, because, depending on the machine used, this could be the cascaded or the tapped density, somewhat in-between, or even a larger density.

In general, if adjustments are made (e.g., if a trial of the filled capsule does not give the correct weight, the remedy is to adjust Y , so that it becomes correct). As has been seen in Chap. 16, apparent densities of mixtures depend on the state of subdivision of the two (or more) ingredients, so that some measure of *machine adjustment* must be available to allow for fill-weight variations that will occur from batch to batch of raw material used. If the fill weight is approximately correct, then machine speed, as mentioned, may be used to adjust it.

22.4. COMPACTION DURING HARD-SHELL FILLING

If a solid is compressed below its elastic limit, then it will distort a bit, and then return to its original shape once the stress is released (Fig. 22.7a).

Compaction is actually resorted to, to some degree, in all of the different types of capsule machines. When a powder is “compressed” gently, it will then remain within the elastic limit. Figure 22.7 demonstrates this, and shows that when a capsule is filled, there is a residual stress, which actually helps keeping the capsule halves together.

There are several aspects to this. The consolidating pressure P , will affect the apparent density. Kawakita and Taneya (1967) have shown that the porosity ε responds to pressure P in the following fashion:

$$\partial\varepsilon/\partial P = c\varepsilon^x \quad (22.6)$$

This integrates to

$$\varepsilon^{x+1}/(x+1) = cP + Q \quad (22.7)$$

where Q is an integration constant that can be derived from the apparent density at zero consolidation pressure. Kawakita and Ludde (1970/71) have compiled a series

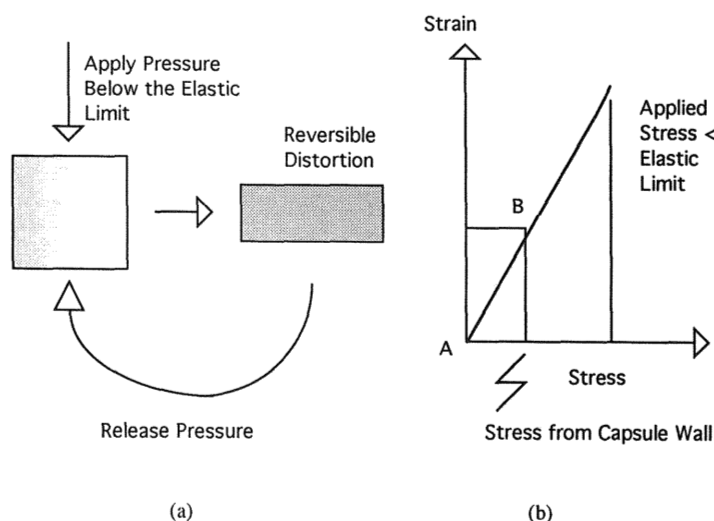


Fig. 22.7 (a) Shapes of a particle under stresses below the elastic limit; (b) Linear stress-strain relation below the elastic limit (Hooke's law).

of consolidation equations. One that has a bearing on compaction equations in Chaps. 23 and 24 is the Cooper equation:

$$\{(V_0 - V)/(V_0 - V')\} = \beta_1 \exp(-\beta_2/P) \quad (22.8)$$

Where V_0 is the volume of the powder at zero pressure, V is the apparent volume at a consolidation pressure of P , and V' is the net volume of the particles. β_1 and β_2 are constants.

22.5. DISSOLUTION AND DISINTEGRATION OF HARD-SHELL CAPSULES

Newton (1972), Newton et al. (1971a,b), and Muhammed et al. (1983) have described the effect of variables in formulation and process on release of drugs in capsule form. The effect of additives and, again, preparation mode on release of active substance from hard-shell capsules has been described (Whithey et al., 1969; Samyn and Jung, 1970; Khalil et al., 1972; Newton et al., 1977, 1980; Stewart et al., 1979).

In fully automated filling machines the powder contents are compressed, so that variables, such as force of compression can affect both dissolution and disintegration. Several authors (Mehta and Augsburger, 1981; Btozolakis et al., 1982, 1984) have investigated the use of disintegrants to improve disintegration and dissolution.

A systematic study of the use of effervescent salt, as compared with conventional disintegrants, in dosator-principle filling machines has been reported by El-Shaboury et al. (1993).

These authors studied effervescent salts as disintegrants as well as conventional disintegrants (Explotab, microcrystalline cellulose). In the former case they found improvement (decrease in disintegration time and t_{50}), when the compression pressure was increased. When their data are plotted as $\ln[M/M_0]$ versus time the plots are not nearly as good (as judged by correlation coefficients) as when a cube-root relation is used (Fig. 22.8). Denoting by M the amount of drug not dissolved, and by M_0 the initial amount, then:

$$1 - [M/M_0]^{1/3} = K(t - t_i) \quad (22.9)$$

where t is time, t_i is lag time, and K is the cube-root dissolution rate constant. This may be recast as

$$[M/M_0]^{1/3} = 1 + Kt_i - (Kt) \quad (22.10)$$

The disintegration time can be deduced from these curves: the intercept minus 1, divided by the value of K . For instance, for the data for 10-kg pressure, the disintegration time would be $0.1695/0.015894 = 10.66$ min. When these are plotted versus disintegration times from conventional disintegration tests, then Fig. 22.9 results.

It is not always, however, that cube-root relations hold best. Data by Tan and Gan (1998) plot better in the semilogarithmic fashion (Fig. 22.10). Cube-root relations may be expected when the capsule contents, once the tablet has disintegrated, presents itself as a particulate powder, whereas plugs or agglomerates will behave in

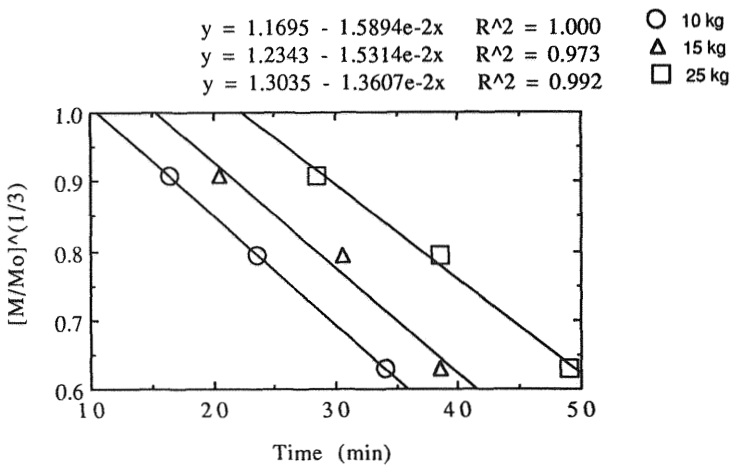


Fig. 22.8 Dissolution of fenopropfen capsules dosator-compacted at different forces. The capsules depicted have no disintegrant or effervescent salt added.

semilogarithmic fashion, because moisture must penetrate the aggregates, dissolve the drug, which then can diffuse out.

In overlubricated powders, disintegration of the shell may occur, but the powder mass will remain intact, and penetration of liquid into a (now hydrophobic) plug gives rise to a slower dissolution. This type of dissolution is likely to follow a square-root law (Higuchi, 1963).

22.6. PELLICULATION

In properly formulated capsules the dissolution steps are (a) rapid dissolution of the shell, followed by (b) dispersion of the powder, followed by (c) dissolution of the drug from distinct drug particles. This type of dissolution curve should simply be a cube-root law, maybe with a slight lag time.

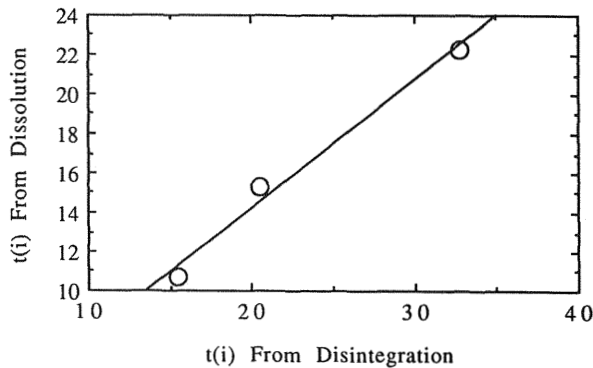


Fig. 22.9 Disintegration values from dissolution plotted versus disintegration from conventional disintegration tests.

$$y = 0.29471 - 9.4256e-2x \quad R^2 = 1.000$$

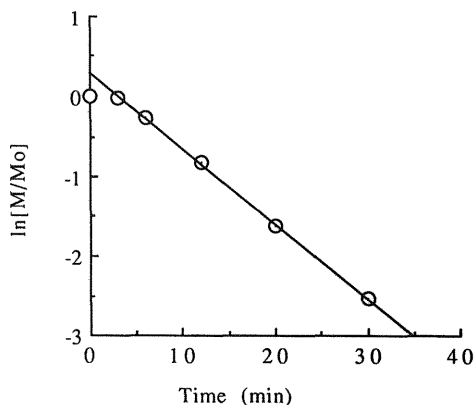


Fig. 22.10 Dissolution of ciprofloxacin HCl capsules. (Data from Tang and Gan, 1998.)

Capsule powders that contain substances with aldehyde or keto groups may experience dissolution rate decrease on storage because of a Maillard-type reaction with the amino groups of the gelatin:



When this occurs, the capsule, when introduced into the dissolution vessel, will form a film (a pellicle or pellicule), which encases the capsule and prevents the drug in it from dissolving.

22.7. SUSTAINED-RELEASE HARD-SHELL CAPSULES

Hard-shell capsules are often used for coated beads and pellet sustained-release dosage forms. The most important aspect of these, owing to their sustained-release nature, is their dissolution pattern.

The common apparatus used is U.S. Pharmacopeia (USP) either method I (basket) or II (paddle). Most common dissolution media are (a) N/10 HCl and (b) water, but some investigators (e.g., Kumar and Pandit, 1997) employ an acid medium at first, and then, at various time periods increasing the pH. For compounds such as ibuprofen, which have higher solubilities at higher pH values, the rate will increase as time (pH) progresses.

Increasing the pH as a function of time in this fashion, the so-called stepped-pH dissolution can be accomplished in different manners (Marty et al., 1997). The pH is usually increased from that of stomach (pH = 1.2) to that of intestine (pH = 7.5).

Two of the methods used to accomplish this involve a total exchange of medium, whereas a third (half-change method) requires exchanging one-half of the liquid with liquid of a higher pH (Brossard and Wouessidjewe, 1990; Münzel, 1960; Ritchel and Orth, 1967). These methods are rather impractical, and there have been other suggested methods for increasing the pH. Marty et al. (1997), Baudy et al. (1989), and Brossard (1976) have used a solid buffer addition to adjust the pH. Sallans et al.

(1988) have suggested a method for which initially one-half of the final volume is used, and liquid addition of buffers then adjusts the pH upward.

SYMBOLS

- a = throat length of hopper
 c = coefficient in pressure/fill equation
 D = fill weight
 K = Hixson–Crowell cube-root constant
 M = mass (weight) of drug not dissolved
 M_0 = initial mass of drug
 P = pressure on fill during filling
 R = radius of die table
 Q = constant in pressure/fill equation
 t = dissolution time
 t_l = lag time
 V_0 = the volume of the powder at zero pressure
 V = (a) apparent powder volume at a consolidation pressure of P ; (b) volume of capsule
 V' = net volume of the particles
 v = linear speed of body of capsule in die
 W = flow rate (g/s)
 X = drug content
 Y = excipient content
 ε = porosity
 β_1 = constant in Cooper–Eaton equation
 β_2 = constant in Cooper–Eaton equation
 τ = dwell time
 Ω = rotations per second (rps) of the die table

REFERENCES

- Bannier A, Brazier JL, Ribon B, Quincy C (1980). *J Pharm Sci* 69:763.
Botzolakis JE, Ausburger LL (1984). *J Pharm Pharmacol* 36:77.
Botzolakis JE, Small LE, Augsburger LL (1982). *Int J Pharm* 12:341.
Brossard C (1976). *Sci Technol Pharm* 5:353.
Brossard C, Wouessidjewe D (1990). *STP Pharma* 6:728.
El-Shaboury MH, El-Gawad AHA, Gabr KE, Hashem FM (1993). *Pharm Ind* 55:175.
Gaudy D, de Albuquerque M, Baylac G, Puech A, Jacob M (1989). *STP Pharma* 5:750.
Higuchi T (1963). *J Pharm Sci* 52:1145.
Kawakita K, Ludde KH (1970/71). *Power Technol* 4:61.
Kawakita K, Taneya S (1967). *Powder Technology*. Plant Kogaku Sha, Tokyo, p 71.
Khalil SA, Ali LM (1972). *Acta Pharm Suec* 9:563.
Khan KA, Rhodes CT (1975). *J Pharm Sci* 64:166.
Kumar DS, Pandig JK (1997). *Drug Dev Ind Pharm* 23:987.
Marty P, Pinteur B, de Fenin V, Aiache J–M (1997). *Drug Dev Ind Pharm* 23:1135.
Mehta AM, Augsburger LL (1981). *Int J Pharm* 7:327.
Muhammed NAH, Newton JM (1983). *J Pharm Pharmacol* 35:345.
Münzel K (1960). *Arch Pharm* 293:766.

- Newton JM (1972). *Pharm Weekbl* 107:485.
- Newton JM, Bader F (1980). *J Pharm Pharmacol* 32:167.
- Newton JM, Razzo FN (1977). *J Pharm Pharmacol* 29:248.
- Newton JM, Rowley G, Tornblum JFV (1971a). *J Pharm Pharmacol* 23:452.
- Newton JM, Rowley G, Tornblum JFV (1971b). *J Pharm Pharmacol* 23:156S.
- Ritchel WA, Orth H (1967). *J Pharm Sci* 56:773.
- Sallans F, Rodriguez F, Sablayrolles A, Combes J, Patau P, Rouffiac R (1988). *J Pharma Belg* 43:81.
- Samyn JC, Jung WY (1970). *J Pharm Sci* 59:169.
- Stewart AG, Grant DJW, Newton JM (1979). *J Pharm Pharmacol* 31:1.
- Tang Y, Gan K (1998). *Drug Dev Ind Pharm* 24:549.
- Whithey RJ, Mainville CA (1969). *J Pharm Sci* 58:1120.

RECOMMENDED READING

- Hostetler V (1986). In: Lachman L, Lieberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Lea & Febiger, Philadelphia, pp 374–394.

23

Tablet Physics

23.1. Principles of Single-Punch Tablet Machines	388
23.2. Principles of Rotary Machines	389
23.3. Multiple-Layer and Compression-Coated Tablets	390
23.4. Stress and Strain: Hooke's Law; Bonding in Tablets	391
23.5. Athy–Heckel Plots	393
23.6. The Cooper–Eaton Equation	394
23.7. Compression Cycles	396
23.7.1 Mohr Bodies	398
23.8. Lubrication	400
23.9. Energy Considerations in Compression	401
Symbols	404
References	405
Recommended Reading	405

As mentioned in the introduction, this text is not geared toward the actual machine and operational details of a solids operation, and only a cursory overview of tablet machines will be given here. This overview is necessary for the further discussion of properties of solids relative to compression.

For further details the reader is referred to the recommended reference texts before the reference list at the end of the chapter for details on tablet machines, methods of instrumentation, and granulation techniques.

23.1. PRINCIPLES OF SINGLE-PUNCH TABLET MACHINES

The *single-punch tablet machine* (or eccentric press) is schematized in Fig. 23.1. In frame A, the hopper is in position over the empty die, bordered below by the bottom punch, and powder flows from the hopper into the die. The amount of powder that flows in is the volume ($V \text{ cm}^3$) times the cascaded apparent density ($\rho' \text{ g/cm}^3$) of the powder, so that the fill weight of the tablet, $U \text{ g}$, is given by:

$$U = V\rho' \quad (23.1)$$

If the fraction of the powder consisting of drug is F , then the dose $D \text{ g}$, is given by

$$D = FV\rho' \quad (23.2)$$

It is obvious that the accuracy and precision of the dose are a function of the accuracy and precision of the fill weight W , and the precision and accuracy of the fraction F . *Content uniformity*, hence, is a function of both these factors.

It is obvious that the fill may be adjusted by the position of the lower punch in the first phase (frame A).

In Fig. 23.1B, the hopper has swung away, and the top punch comes down and compresses the powder into a tablet. The dimensions of the tablet are a function of the longest path this punch takes, and this can be adjusted, so that the *thickness* of the tablet may be adjusted in this way. This also adjusts the *hardness* of the tablet. Hence, in general, in tablets made on a single-punch machine, there is a functional relation between the thickness and the hardness.

Single-punch machines produce, at top speed, about 60 tablets per minute. If the number of tablets per second is denoted N , then the amount of powder flowing into the die per minute is

$$W = NU \text{ g/s} \quad (23.3)$$

W is the required flow rate for the powder. Because most powders have flow rates in excess of 60 g/s there is *generally* no problem with the powder flowing into the die sufficiently rapidly (see Fig. 23.1A). It shall be seen, under rotary presses, that this becomes a problem as the dwell time becomes smaller. The *dwell time* τ s is given by

$$\tau = q/N \quad (23.4)$$

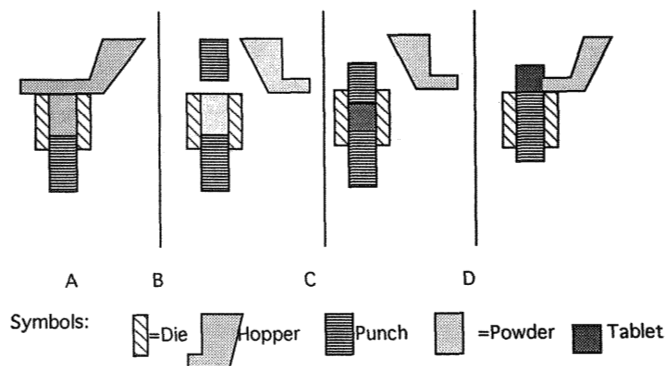


Fig. 23.1 Principle of single-punch tablet machine.

where q is the fraction of the cycle (see frames A–D) the hopper stays in the position of frame A.

23.2. PRINCIPLES OF ROTARY MACHINES

Single-punch machines are slow and are used mostly in product development and in initial clinical trial batches when raw material (drug substance) is in low quantity.

When larger quantities are required, rotary machines are resorted to, and essentially all manufacturing equipment is of the rotary type.

In a simple setup (Fig. 23.2), a hopper feeds powder into a feed frame, under which dies and lower punches receive the powder (Fig. 23.3). Once outside the feed frame the upper punch descends and its downward movement, in combination with the upward movement of the lower punch, produces the tablet. As opposed to a single-punch machine this is referred to as double-sided compression.

The tablet, ejected from the die by the extreme upward movement of the lower punch is removed from the die table at the end of the circle at the back of the hopper (the knockoff bar), and the cycle repeats.

Many high-speed machines are equipped with two or three hoppers, around the periphery at 120° angles (Fig. 23.4).

Some requirements are apparent from the general setup. It is economically desirable to operate the machine at as high a speed (λ rps; rotations per second) as possible. One of the limiting quantities is the flow rate of the powder.

If the radius of the die table is denoted R , then the linear speed of the dies is $2\pi\lambda R$; hence, the dwell time is

$$\tau = a/2\pi\lambda R \tag{23.5}$$

With a required fill weight of U , it follows that the required flow rate W is given by

$$W = U/\tau = U2\pi\lambda R/a \tag{23.6}$$

or, because the machine operation is adjustable and, for a given powder, W is not (without further manipulation) changeable, the maximum allowable machine speed would be

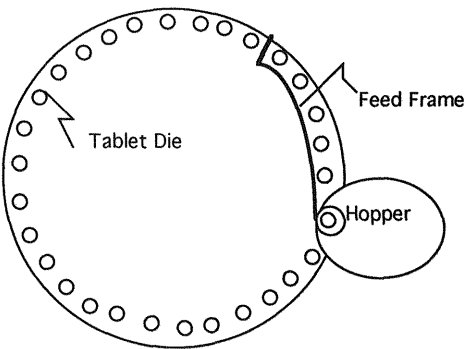


Fig. 23.2 Schematic of rotary machines.

$$\lambda_{\max} = Wa/U2\pi R \quad (23.7)$$

This is *one* of the flow rate requirements of the powder. If there are N stations to be filled under the feed frame, and the flow rate from hopper to feed frame is L g/s then the lag time must be at least

$$\tau = NU/L \quad (23.8)$$

Inserting this in Eq. 23.5 then shows that the maximum machine speed would be:

$$\lambda_{\max} = aL/(U2\pi R) \quad (23.9)$$

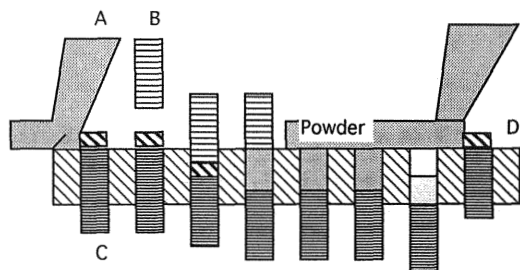
The smaller of the two λ -values in Eqs. (23.6) and (23.8) is the limiting speed at which the machine can be operated and still produce weight-quality product.

Powder flow has been treated in Chap. 18, but it should be mentioned at this point (Carstensen and Laughlin, 1979; Laughlin et al., 1979) that flow rates are dynamic in a sense, in that the powder in the feed frame differs from the static flow rate experienced when a powder flows through an orifice of a stationary hopper.

23.3. MULTIPLE-LAYER AND COMPRESSION-COATED TABLETS

At times, it is necessary to “separate” two components of a solid-dosage form. It could be a case of physical or chemical incompatibility, and a classic example of this is methypyrlyon and caffeine (Carstensen, 1977), for which the two compounds form very low temperature eutectics. An example of chemical incompatibility is aspirin and dialminate.

One manner in which such a separation may be accomplished is by way of either a double-layer tablet or a triple-layer tablet. In the latter, the layout is, as shown in Fig. 23.4, three hoppers are placed at 60° angles to one another, and three granulations, A, B, and C are placed in the appropriate hoppers. A is first filled into dies in a feed frame between A and B, and loosely compacted, granulation B is then filled into the die as it passes hopper B and compressed a bit harder between hoppers B and C, and then finally C is filled into the die as it passes hopper C and the final, desirable pressure is applied. The tablet is then ejected at a knockout bar at the back of hopper A.



Legend: A = Hopper, B = Upper Punch,
C = Lower Punch, D = Tablet

□ = Loose Powder ■ = Denser Powder

Fig. 23.3 Schematic wrapped-out view of punch positions during the compression on a rotary machine.

Pressures and speeds are adjusted so that the layer separations are “clean,” particularly if the layers have different colors. The two incompatible compounds, in the foregoing examples, would be in granulations A and C. If the incompatibility is *physical* (e.g., by way of eutectic formation), there may still be interaction in the packed product, if it is simply packed (in random arrangement) in a bottle. In that event, there will be contact point between tablets, and whenever layer A from one tablet touches layer C of another, there may be a “spot” occurring.

Two-layer tablets are employed when the incompatibilities are less pronounced. In that case there will always be interaction in the contact area between the two layers. In two-layer tablet manufacture there are only two (or four) hoppers.

In more pronounced situations of incompatibility, or when special release effects are desired, triple-layer tablets may be resorted to (Fig. 23.4) or, bicoated or tricoated tablets are a solution. It is not used often, primarily because of the complicated nature of the construct, and the associated lower tablet machine speeds. The principle of a bicoated tablet is shown in Fig. 23.5.

Figure 23.5 shows one end of a die table. A die is first half-filled with the outer granulation (A), and a tablet is dropped into it (B), it is then filled to the top with outer granulation (C), and compressed (D).

The process is slow (800 tablets per minute), but for incompatible drugs it may be a last resort. Tablets-within-tablets-within tablets (tricoating) also is possible, and here totally incompatible components can be separated by a neutral layer (see Fig. 23.5).

Thomas et al. (1998) have described how the core material properties affect the compression and the properties of compression-coated tablets made with microcrystalline cellulose as the coating material.

23.4. STRESS AND STRAIN: HOOKE'S LAW; BONDING IN TABLETS

Hiestand states that the mechanical criteria for a successful tablet formulation are good flowability for powders and adequate strength without fracture for compacts. The matter of flow has already been discussed, but further aspects of it will be dealt

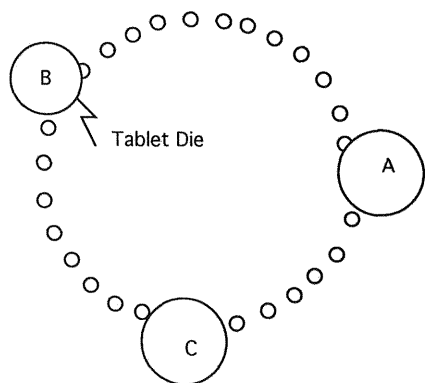


Fig. 23.4 Schematic of triple-layer tablet turret.

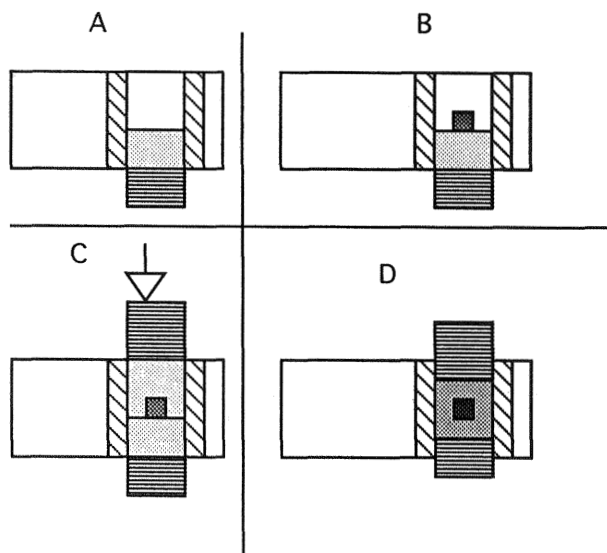


Fig. 23.5 Principle of bicoating (tablet within a tablet).

with in the following. The aspect of strength of materials and of compacts will also be discussed.

It has been seen in previous chapters that efforts are made to make particles “round,” and sufficiently large, so that they will flow well, and add binders, so that they will bond when they are compressed. This entails wetting the powder, and then removing the water by drying operations, and as such is energy-inefficient. It is also labor-intensive and, in the 1960s, there was a sustained and successful attempt to accomplish tableting of drug substances by simply mixing them with excipients and compressing them.

Tableting is carried out by applying (compressional) stress to a powder bed. The intent is, by causing close proximity between the molecules in one particle to those in another, to create a “chemical” bond. To this end the surface molecules must be distant by no more than molecular dimension distances. Carstensen (1977, 1981), among others, has shown that the steps, involved in the tableting are (a) elastic deformation, (b) plastic deformation, and (c) fracture (Fig. 23.6). It is one of the two latter steps that is responsible for bond formation.

If, as exemplified in Fig. 23.6 a cubical block is exposed to a pressure P , then it will “give” (i.e., it will become thinner and wider). Up to a certain pressure, $P(1)$, this is reversible (i.e., if the pressure is released then the original form will be regained). The solid, in this range of pressures, is said to exhibit elasticity.

Once $P(1)$ (see Fig. 23.6) is exceeded (point B Fig. 23.7), the deformation becomes irreversible (i.e., if the pressure is lifted, the solid will relax, but it will not return to its original shape). This is denoted the elastic limit or yield value. Beyond this point, further increases in pressure may then result in further deformation (see portion BC in Fig. 23.7). If the pressure is released at any point in this portion, then the block will remain intact; but will be distorted. At a given pressure, $P(3)$ (see point C in Fig. 23.7) breakage will occur, and this is denoted brittle frac-

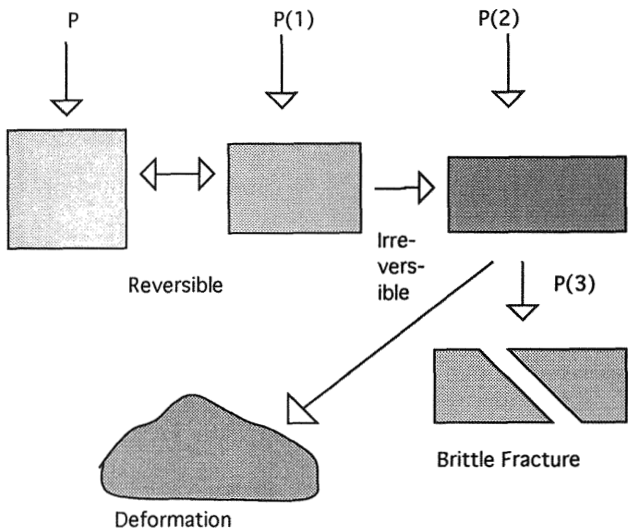


Fig. 23.6 Schematic of yield and fracture of a block.

ture. This is shown, graphically, in Fig. 23.7, which has been shown earlier and is repeated here for convenience.

Often, the portion BC is small, and the bond formation that occurs in this region is insufficient to make a “good” compact, so the pressure has to be brought all the way up to $P(3)$ for good bonding to occur. This situation is denoted bonding by brittle fracture. If, however, adequate bonding between particles occurs in the region BC in Fig. 23.7, then bonding is said to occur by plastic deformation.

The slope of the line AB is denoted the Poisson’s ratio, ν . Robers et al. (1994) have determined the Poisson’s ratio for microcrystalline cellulose.

23.5. ATHY–HECKEL PLOTS

Up to a certain limit of compression pressure, tablets will become thinner; the higher the compression pressure, the thinner the tablet will become.

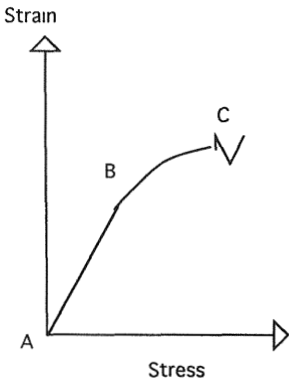


Fig. 23.7 Strain versus stress profile.

The thinner it is, the smaller the porosity (ε) and the so-called Athy–Heckel (or simply Heckel) equation states that

$$-\ln[\varepsilon] = aP + b \tag{23.10}$$

where a and b are constants (Heckel, 1961).

Table 23.1 and Fig. 23.8 show thickness data of a tablet as a function of compression pressure. The tablet has a cross-sectional area of 1 cm^2 and the true density of the contents is $\rho = 1.5\text{ g/cm}^3$. The fill weight is 900 mg, so that if there were no porosity at all, then the thickness h of the tablet would be given by

$$h = 0.9/1.5 = 0.6\text{ cm} = 6\text{ mm} \tag{23.11}$$

so that, at a thickness of 0.60, all the porosity is gone (i.e., the tablet is simply solid). Knowing the thickness at any given compression pressure, a similar procedure will give the apparent density ρ' , so that the porosity ε can be calculated from

$$\varepsilon = 1 - \{\rho'/\rho\} \tag{23.12}$$

The thicknesses in Table 23.1 are the experimental value, and the calculated porosities are shown in the third column of the table, The negative of its logarithm is then shown in the fourth column.

The *negative* of the natural logarithm of the porosity is plotted versus applied pressure in Fig. 23.8, and the data linearize. It is strictly an arbitrary convention in literature to plot $-\ln[\varepsilon]$ rather than $\ln[\varepsilon]$. If the latter were done, then the data would still be linear, but with a positive slope.

Heckel (1961) found, experimentally, that the slopes of such plots are $1/(3\phi)$ where ϕ denotes yield value. The data in Table 23.1 are plotted in Fig. 23.9, and it is seen that $1/3\phi = 0.66$, so that the yield value is calculated to be $\phi 1/(3 \times 0.66) = 0.5\text{ ton/cm}^2$.

23.6. THE COOPER–EATON EQUATION

Linearity in the Athy–Heckel equation is always somewhat lacking. Cooper and Eaton (1962) improved on this by assuming that two processes were at play in the compression. The compression would first, through rupture of particles and their percolation, fill larger void spaces in the powder bed, and once that process was over,

Table 23.1 Example of Porosity as a Function of Applied Pressure

Compression pressure (tons/cm ²)	Thickness (cm)	Porosity	$-\ln[\text{Porosity}]$
2000	2.4	0.4	0.916
2500	1.35	0.5	1.067
4000	0.68	0.118	2.137
5000	0.64	0.062	2.781
6000	0.62	0.032	3.442
7000	0.61	0.016	4.135
(8000)	0.60	0	

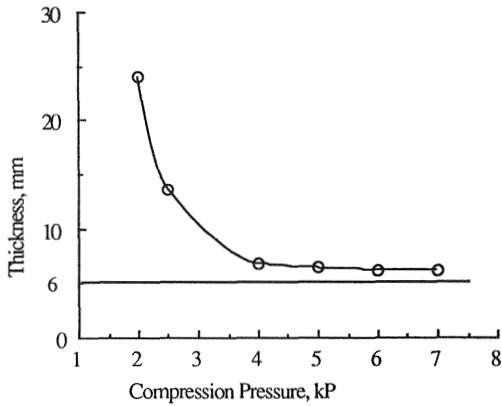


Fig. 23.8 Data in Table 23.1 plotted linearly.

it would repeat, and the now smaller particles would rupture and fill the “smaller” void spaces. This led to a compression profile that was best described by fractional volume compression.

$$(V_0 - V)/(V_0 - V^*) = a \exp(-k_1/P) + b \exp(k_2/P) \tag{23.13}$$

where V_0 is volume before compression, V is volume at a pressure P , and V^* is the volume corresponding to true density; a and k_1 are constants relating to the first fracture and percolation, and b and k_2 are constants relating to the second step. An example of the trace produced by such an equation is shown in Fig. 23.10.

When P tends toward infinity, the exponents tend toward zero, so that the exponential values approach 1.0; hence, the curve in Fig. 23.10 has an asymptote at $(V_0 - V)/(V_0 - V^*) = 0.5 + 0.5 = 1.0$, which is what it should be ($V = V^*$). Chowhan and Chow (1981b), showed that for naproxen and HPMC the equation gave a more rational fit than the Heckel equation (Fig. 23.11).

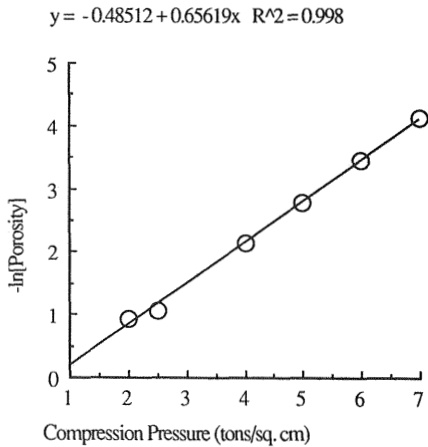


Fig. 23.9 Data in Table 23.1 plotted by the Athy–Heckel equation.

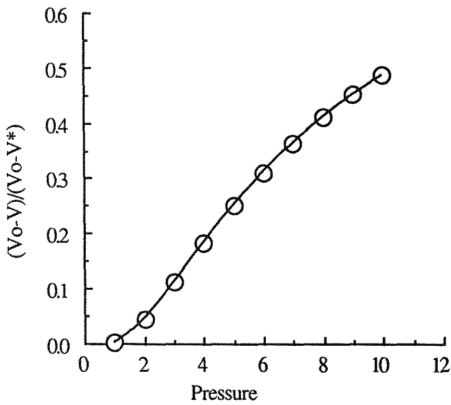


Fig. 23.10 Trace of the equation $(V_0 - V)/(V_0 - V^*) = 0.5 \exp(-5/P) + 0.5 \exp(-10/P)$.

23.7. COMPRESSION CYCLES

If a powder mass is confined in a cylindrical space, and a force is exerted on the top of it, it might, at first sight, seem that the downward force would simply be propagated through the mass, and the reactive force on the bottom of the space would be equal and opposite the force exerted on the top. However, Fig. 23.12 shows, schematically, how some of the force is “diverted” to the walls of the confining space.

In the diagram the hypothetical situation of a “powder mass” of five spheres arranged as two, one, and two is presented. The downward force is A and B, which is then decomposed in EC and DF, toward the wall, and CG and DG toward the center of the sphere in the second layer. This force is propagated along the same center line to the two spheres in the bottom layer GQ and GH, and these are decomposed into wall forces HJ and QK and the downward forces HL and QM.

During the compression there will be work exerted, and part of this work will be “lost” to the die wall. This will be touched on further under Sec. 23.8, *Lubrication*. The diagram explains the so-called Uncle equation, that the downward pressure, P_z ,

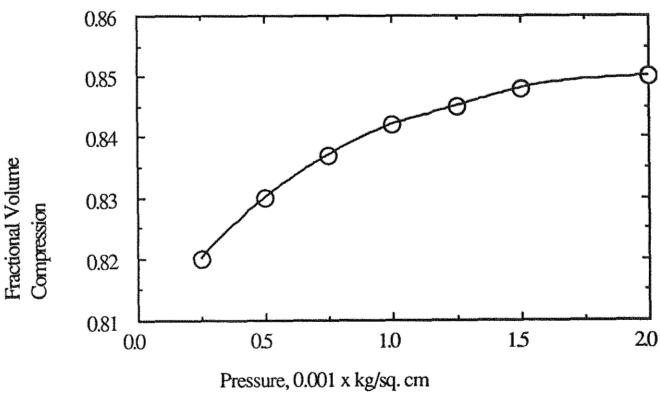


Fig. 23.11 Example of data that would fit the Cooper–Eaton equation. (Data from Chowhan and Chow, 1981.)

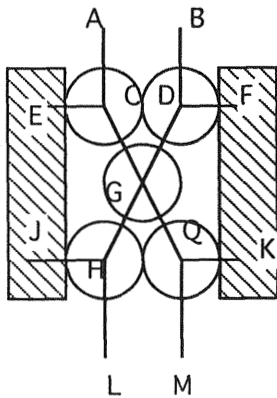


Fig. 23.12 Schematic showing die wall force.

decreases through the compression mass as a function of the distance x , from the surface by the relation:

$$P_{<} = P_u \exp(-kx) \tag{23.14}$$

Higuchi et al. (1953) were the first to instrument a tablet machine, so that the pressures on the upper and lower punches and on the die wall could be monitored during a compression cycle. This will be shortly dealt with here. A fair amount of older literature on this subject deserves mentioning; namely, that of Long, 1960; Schwartz and Weinstein, 1965; Perelman and Roman, 1971; Schwartz and Holland, 1969; Koerner and McCabe, 1972; Paris et al., 1975; Leigh et al., 1967; and Strijbos et al., 1977.

Applied forces are usually referred to by the symbol P , but in discussion the compression cycle in the following, die wall pressure (stress) will be denoted τ , and applied pressure will be denoted σ . If we refer to the upper portion of Fig. 23.13, the first part of the compression cycle (part A) starts at the point when the punches experience a measurable force from the powder. From this point (line OP) on the die wall stress (or pressure) τ is fairly linear relative to the applied pressure (σ ; as visualized in Fig. 23.13, with a slope equal to the Poisson ratio ν , of the powder), that is,

$$\tau = \nu\sigma \tag{23.15}$$

Marshall (1977) has shown, however, that a more realistic representation is:

$$\text{Line segment OP: } \tau = [\nu/(1 - \nu)]\sigma \tag{23.16}$$

As pharmaceutical examples of Poisson's ratio, Robers et al. (1994) have reported on the ratio for microcrystalline cellulose.

The point P in Fig. 23.13 represents the elastic limit. If this is high, then removal of the load will cause the original line (OP) to be regained, and bonding will not occur.

When forces (or pressures) are applied above point P, then bonding will occur through plastic deformation or brittle fracture. One of these will predominate (Carstensen and Touré, 1980).

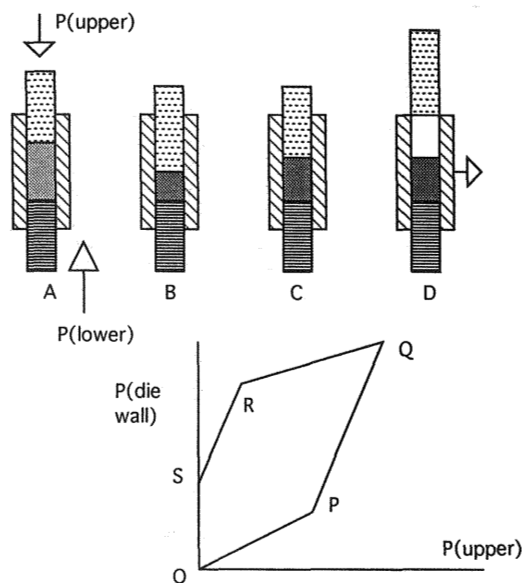


Fig. 23.13 Compression cycle.

If the bonding is by *plastic deformation* (i.e., considering the body viscoelastic), then the solid behaves as a liquid, and if the yield value is denoted ϕ , then the equation for the line segment PQ is:

$$\text{Line Segment } PQ: \tau = \sigma - \phi \quad (23.17)$$

where τ is the stress on the die wall.

Line QR obeys the equation (Parrott, 1990)

$$\text{Line Segment } QR: \tau = (v/(1-v))\sigma + \{1 - (v/(1-v))\}\sigma_{\max} - \phi \quad (23.18)$$

At point R the die wall stress is greater than the applied stress by a value equal to the yield stress so the equation for line RS is:

$$\text{Line Segment } RS: \tau = \sigma + \phi \quad (23.19)$$

Carstensen and Touré (1980) integrated these equations to find the area (OPQRS) within the compression cycle and found it to be linear with $\tau_{\max}$ (i.e., the “applied compression pressure”).

It is noted that the cycle predicts a *residual die wall stress* of ϕ .

23.7.1 Mohr Bodies

Hiestand (1997) also points out that describing the properties of compacts by linear-elasticity equations has limitations, because compacts (in practice) are porous, and they are nonhomogeneous, viscoelastic Mohr bodies.

A Mohr body is a construction showing τ versus σ and, to some degree applies to a powder bed as well as to a solid body. This is akin to the shear loci discussed in Chap. 17.

The shear loci depicted in Fig. 17.7 may be presented in the fashion shown in Fig. 23.14. Mase (1970) points out that “frequently... a state of plane stress is represented by a single Mohr’s circle... this representation is necessarily incomplete since all three circles are required to show the complete stress picture... A single circle Mohr’s diagram is able, however, to display the stress points for all those planes at the point P which include the zero principal stress axis...”

This, notwithstanding, a two-dimensional representation is shown here (as, to my knowledge, it is used in all pharmaceutical publications).

The construct essentially states that when a given normal load is applied to a powder bed, there will then be a plane of maximum stress at an angle of ϕ to the principal stress axis. The tangential component of the stress will be

$$\tau = (\sigma_1 - \sigma_3)/2 \quad (23.20)$$

and the normal component will be

$$\sigma = (\sigma_1 + \sigma_3)/2 \quad (23.21)$$

If total symmetry is assumed, only one Mohr circle then suffices. If the failure is characterized by that of a Mohr body, then the segment OP is still governed by Eq. (23.16).

$$\text{Line Segment OP: } \tau = [v/(1 - v)]\sigma \quad (23.22)$$

If the stress increases beyond C (see Fig. 23.14), then failure occurs. In the plane of shear, τ , in this situation, equals

$$\sigma/2 - \tau/2 \quad (23.23)$$

The tangential stress in excess of C (see QR – NO in Fig. 23.14) is, hence,

$$(\sigma/2 - \tau/2) - C \quad (23.24)$$

The normal stress in the symmetrical situation equals

$$\sigma/2 + \tau/2 \quad (23.25)$$

and recalling that tangential stress equals friction times normal stress then gives

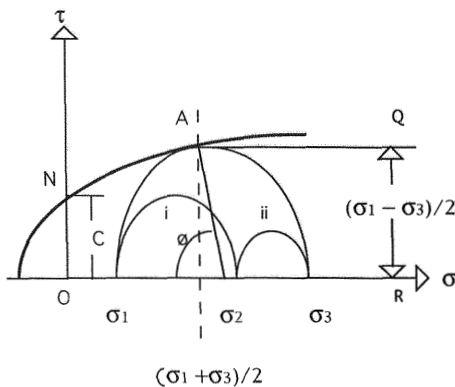


Fig. 23.14 Shear locus and Mohr circles.

$$(\sigma/2 - \tau/2) - C = \mu(\sigma/2 + \tau/2) \quad (23.26)$$

This may be rearranged to express τ as a function of σ , which gives the equation for

$$\text{Line Segment PQ: } \tau = [(1 - \mu)\sigma/(1 + \mu)]\sigma - [(2C)/(1 + \mu)] \quad (23.24)$$

The line segment QR is parallel to line segment OP and passes through the point $(\sigma_{\max}, \tau_{\max})$, where

$$\tau_{\max} = [(1 - \mu)\sigma_{\max} - 2C]/(1 + \mu) \quad (23.25)$$

so that the equation for line segment QR becomes

$$\text{Line Segment QR: } \tau = \{[(1 - \mu)\sigma_{\max} - 2C]/(1 + \mu)\} + \{[\nu(\sigma - \sigma_{\max})]/(1 - \nu)\} \quad (23.26)$$

At one point (point R) the radial stress will exceed the normal stress, and the descent will now be of a Poisson type, with the restriction that it goes through the point where $\sigma = \tau$. The equation for this line is

$$\text{Line Segment RS: } \tau = \{[(1 + \mu)/(1 - \mu)]\sigma - [2C/(1 - \mu)]\} \quad (23.27)$$

It is noted that the residual die wall pressure is obtained by setting $\sigma = 0$; that is, it is

$$\text{Residual die wall pressure: } \{2C/(1 - \mu)\} \quad (23.28)$$

Carstensen and Touré (1980) integrated these equations to find the area within the compression cycle and found it to be proportional to the square of $\tau_{\max}$ (i.e., the “applied compression pressure”).

Such plots, hence, give information on whether bonding occurs primarily through plastic deformation or through brittle fracture.

23.8. LUBRICATION

After completion of the cycle there remains a residual die wall pressure, being the residual force $F(d)$, divided by the area of the wall. The definition of frictional coefficient is recalled, and is exemplified in Fig. 23.15.

To eject the tablet, a certain ejection force E is necessary. The residual die wall force, $F(d)$ in Fig. 23.15 is the normal force and E is the tangential force, so that the definition of frictional coefficients gives

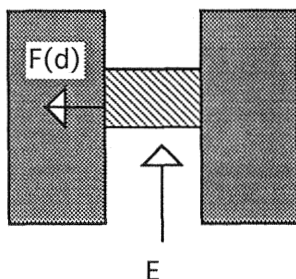


Fig. 23.15 Example of the definition of frictional coefficient.

$$E = \mu F(d) \tag{23.29}$$

where μ is the frictional coefficient between the die wall and the tablet mass.

There have been attempts in literature to assess the frictional coefficient between a compressed powder mass and adjoining metal (Carstensen et al., 1980).

Higuchi (1954) suggested that the ratio between upper F_u and lower punch pressure F_l , the so-called F-ratio, was an indication of the lubrication efficiency of the formulation; that is, the closer the ratio

$$F_{\text{Higuchi}} = F_l/F_u \tag{23.30}$$

is to unity, the better the formula is lubricated. Guyot et al. (1977) suggested that work on the lower punch divided by the energy input of the upper punch in the compression cycle would be a better index.

If the thickness of the compressional mass is denoted h , then combining Eq. (23.30) with the Unckel equation then yields

$$F_{\text{Higuchi}} = R = (F_u \exp(-kh)/F_u = \exp(-kh) \tag{23.31}$$

23.9. ENERGY CONSIDERATIONS IN COMPRESSION

By means of displacement gauges, it is possible to monitor upper punch, F_u and lower punch, F_l , forces and at the same time measure the depth of the upper punch intrusion (on a single-punch machine). When such traces are obtained, profiles such as shown in Fig. 23.16 result.

During compression a curve, such as OA, will be obtained, and after pressure is released a curve, such as AB, will be obtained. Work equals force times distance, so that the compression work or energy W_c , is given by

$$W_c = \text{area OADO} = \int_0^A f_1(x)dx \tag{23.32}$$

The energy lost (the elastic energy, W_e) after the pressure is released is given by

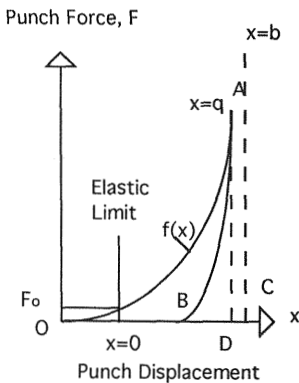


Fig. 23.16 Force–displacement plot.

$$W_e = \text{area BADB} = \int_B^A f_2(x)dx \quad (23.36)$$

so that the total energy or work, W_{total} imparted on the tablet after the cycle is complete is given by

$$W_t = \text{area OADO} = \int_0^A \{f_1(x) - f_2(x)\}dx \quad (23.37)$$

The first part of the compression event is a consolidation below the elastic limit (F_0) The energy consumption in this area is relative small. Beyond this limit, there will be a substantial amount of work needed for further invasion of the upper punch, and brittle fracture or plastic deformation of the particles will take place. The deepest invasion of the upper punch is denoted $x = q$ in Fig. 23.16.

The force displacement profile is denoted $f(x)$ in Fig. 23.16, and Führer (1965) and Parmentier (1974) suggested that $f(x)$ was hyperbolic, asymptoting at $x = b$. Hence, the force equation would be

$$F = F'/(b - x) \quad 0 \leq x < b \quad (23.38)$$

where F' is a characteristic constant. From this it follows that

$$F' = F_0 b \quad (23.39)$$

and, hence,

$$F = F_0 b/(b - x) \quad (23.40)$$

Data treated in the logarithmic form of this (Fessi et al., 1981) are shown in Fig. 23.17. The fit is good, although the slope differs from negative unity.

In Fig. 23.16, the maximum applied force F^* (occurring at $x = q$) is

$$F^* = F_0 b/(b - q) \quad (23.41)$$

Eq. 23.40 may be written:

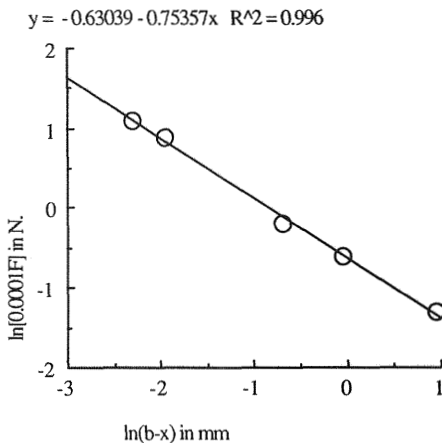


Fig. 23.17 Diphenhydramine hydrochloride tablets containing 50% polyvinyl polymer. (Data from Fessi et al., 1981.)

$$\ln F = -Q \ln(b - x) + \beta \tag{23.42}$$

where β and Q are constants.

Since work and intrusion distance are correlated by

$$dW = Fdx \tag{23.42}$$

it follows that the energy imparted on the tablet is

$$W_e = \int_0^q F_0 b / (b - x) dx = F_0 b \{ \ln \{ b / (b - q) \} \} \tag{23.43}$$

Referring to Fig. 23.6 and introducing Eqs. (24.40) and (23.41) into Eq. (23.43) then gives

$$W_e = F_0 b \ln[F^*] - F_0 b \ln[F_0] \tag{23.44}$$

This predicts W_e (energy) when plotted versus $\ln[F^*]$ should give a linear trace, and that the slope to intercept ratio should be $-\ln[f_0]$. *It is noted that this is a means of obtaining the elastic limit of the tablet powder.*

Figure 23.18 shows data by Fessi et al. (1981) treated by way of Eq. (23.44).

It may be seen that the slope/intercept ratio gives

$$\ln[F_0] = 122/14.15 = 8.6 \tag{23.45}$$

so that

$$F_0 = \exp(8.6) = 5900N \tag{23.46}$$

To obtain the stress at the elastic limit, this number would have to be divided by the area over which the force is in effect. A formal way of doing this is to obtain the porosity ε of the fill at this force (which may be done from the length of intrusion at the given value of F_0) and then assume that the force works over an area of $A\varepsilon$.

The mean yield pressure (MYP) has been reported for formulations. Duberg and Nyström (1985) determined that when microcrystalline cellulose (MCC; Avicel 100) is present with such compounds as lactose and acetaminophen (paracetamol),

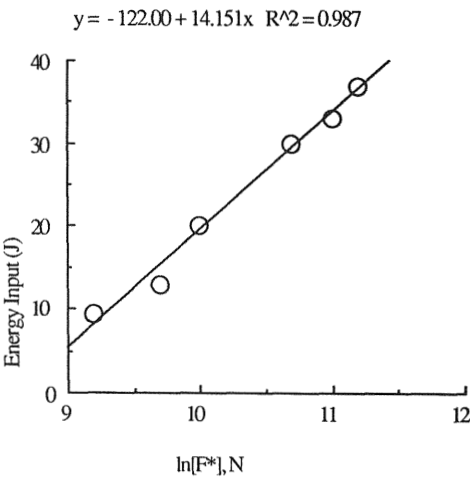


Fig. 23.18 Energy plotted against $\ln[F^*]$. (Data from Fessi et al., 1981.)

the MYP decreased in a linear fashion with MCC concentration. Lahrib and Wells (1998) showed that at low PEG concentrations (mixed with dicalcium phosphate), the MYP decreased linearly with polyethylene glycol (PEG) concentration.

SYMBOLS

- A = cross-section of a tablet (cm^2)
 a = (a) length of feed frame; (b) slope of a Heckel plot
 b = (a) intercept of a Heckel plot; (b) punch depth at which porosity is zero
 C = cohesive stress
 E = ejection force
 F = fraction of fill that is drug
 F' = force constant in Fessi equation
 F = force sensed by punch during compression cycle
 F^* = maximum force during compression
 F_1 = lower punch force
 F_u = upper punch force
 F^* = maximum applied force occurring at $x = q$
 $F(d)$ = residual die wall force
 $f(x)$ = function describing punch force as a function of punch depth
 D = dose
 h = thickness of a tablet (cm)
 k = rate constant in the Unckel equation
 k_1, k_2 = rate constants in the Cooper–Eaton equation
 N = number of tablets per second
 P = pressure
 $P_<$ = pressure at a point x below the tablet reference plane
 P_u = pressure at upper punch
 q = fraction of the cycle the hopper stays over the die
 Q = constant in the Fessi equation
 q = see F^*
 R = (a) radius of die table; (b) $R = F_1/F_u$ = Higuchi R ratio
 rps = rotations per second
 U = fill or tablet weight
 V = (a) die volume; (b) fractional volume of a powder at a given pressure P
 V_0 = fractional volume of a powder at the point of closest packing
 V^* = volume at infinite pressure
 W = (a) required flow rate; (b) total energy imparted to a tablet during compression
 W_e = elastic energy lost after removal of upper punch
 W_c = work imparted during compression
 W_f = total energy imparted on tablet after the cycle is complete
 x = distance in tablet mass from upper punch surface
 β = constant in the Fessi equation
 ε = porosity
 λ = rotational speed (rps)
 μ = frictional coefficient
 ν = Poisson's ratio

σ = normal stress

ϕ = yield value for viscoelastic solid

ρ = particle density

ρ' = apparent density

$\sigma_{\max}$ = maximum stress in a compression cycle (compression pressure)

σ_1 = minor stress component of normal stress in two-dimensional Mohr circle

σ_3 = major stress component of normal stress in two-dimensional Mohr circle

τ = (a) dwell time; (b) shear stress

REFERENCES

- Carstensen JT (1980). *Solid Pharmaceuticals: Mechanical Properties and Rate Phenomena*. Academic Press, New York, p 170.
- Carstensen JT, Laughlin SM (1979). *Powder Technol* 23:79.
- Carstensen JT, Tourée P (1990). *Powder Technol* 26:199.
- Chowan ZT, Chow YP (1981). *Int J Pharm Technol Prod Manuf* 2:29.
- Cooper AR, Eaton LE (1962). *J Am Ceramic Soc* 45:97.
- Duberg M, Nyström C (1985). *Int J Pharm Technol Prod Manuf* 6:27.
- Fessi H, Marty J-P, Puisieux F, Carstensen JT (1981). *J Pharm Sci* 70:1005.
- Führer C (1965). *Dtsch Apoth Ztg* 105:1150.
- Heckel RW (1961). *Trans Metallurg Soc AIME* 221:671, 1001.
- Higuchi T (1954). *J Am Pharm Assoc Sci Ed* 43:344.
- Koerner RM, McCabe WM (1972). *Proc 1972 Powder Metallurg Conf* pp 225–241.
- Lahrib H, Wells JI (1998). *Int J Pharm* 160:197.
- Laughlin SM, Carstensen JT (1981). *J Pharm Sci* 70:711.
- Laughlin SM, Van Campen L, Takinddin M, Duchene D, Puisieux F, Carstensen JT (1979). *Int J Pharm* 3:32.
- Leigh S, Carless JE, Burt BW (1967). *J Pharm Sci* 56:888.
- Long WM (1960). *Powder Metallurg* 6:73.
- Mase GE (1970). *Continuum Mechanics*. McGraw-Hill, New York, p 57.
- Parmentier W (1974). Dissertation, Technical University Carlo-Wilhemina zu Braunschweig, Braunschweig, Germany, pp 1–90.
- Paris J, Duchene D, Puisieux F (1975). Presented at the 2nd International Conference on Compression. Brighton, England, Sept 2–4.
- Parrot E (1990). In: Lieberman HA, Lachman L, Schwartz JB, eds. *Pharmaceutical Dosage Forms: Tablets*, vol 2. Marcel Dekker, New York, pp 236–237.
- Perelman VE, Roman OV (1971). *J Powder Metallurg* 9:692.
- Roberts RJ, Rowe RC, York P (1994). *Int J Pharm* 105:177.
- Schwartz EG, Holland AR (1969). *Int J Powder Metallurg* 5:79.
- Strijbos S, Rankin PJ, Klein RJ, Wassink M, Bannick J, Oudemans GJ (1977). *Powder Technol* 18:187.
- Unckel H (1945). *Arch Eisenhüttenwesen* 18:161.

RECOMMENDED READING

- Banker GS, Anderson NR (1986). In: Lachman L, Lieberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*. Lea & Febiger, Philadelphia, pp 293–345.
- Carstensen JT (1984). In: Fayed ME, Otten L, eds. *Handbook of Powder Science and Technology*. Van Norstrand Reinhold, New York, pp 252–269.

This Page Intentionally Left Blank

Physical Principles of Tablets

24.1.	Direct Compression Conditions	408
24.2.	Loading and Particle Size Considerations	409
24.3.	Direct Compression Mechanisms	411
24.4.	Asperite Melting	411
24.5.	Variables	413
24.6.	Direct Compression Excipients	413
24.6.1.	Microcrystalline cellulose	414
24.6.2.	Maltodextrins	414
24.6.3.	Chitosan and xylitol	414
24.7.	Dry Binders	414
24.8.	Mixed Direct Compression Excipients	415
24.9.	Effect of Moisture	415
24.10.	Wet-Granulated Tablets	416
24.11.	Defects in Direct Compression	416
24.12.	Slugging and Roller Compaction	417
24.13.	Hardness (Crushing Strength, Tensile Strength)	418
24.14.	Capping	419
24.15.	Uniaxial Expansion	420
24.16.	Bonding Types	421
24.17.	Optimization	422
	Symbols	424
	References	425
	Recommended Reading	426

Historically, tablets were primarily made by wet granulation. The attributes of flowability, compressibility, and wettability were considered best achievable by means of such a process. That certain products (effervescent tablets, aspirin) would have to be processed dry, led the way to what is known as direct compression. It *is* illogical, to first add water to a mass of powder, and then to remove it, and if it is possible to simply mix powders and compress them, then the process would become less labor-intensive and more economical. Some aspects might be lost (e.g., wettability), it might become more difficult to meet content uniformity standards, but the aspects of economics has made direct compression attractive.

24.1. DIRECT COMPRESSION CONDITIONS

If the yield value of a powder is “low,” then it is often referred to as autocompressible, and it is possible to simply place the powder in a die and compress it, and it will form a tablet (once the yield value has been reached). Such an approach is denoted “direct compression” or simply DC, and excipients that are directly compressible are denoted “direct compression excipients” or DC excipients. However, the powder must also flow well for it to be directly compressible.

If the powder has a high-yield value, higher than practically achievable on a tablet machine, then wet granulation is a means of achieving a compressible formula, because the binder will have a sufficiently low-yield value that bonding can occur.

If the powder itself is *autocompressible*, but does not flow well, then it can be made flowable by wet granulation or, as shall be seen later in this chapter, by slugging or roller compaction. But direct compression without these precompression operations is not possible for powders with very high yield values or poor flow characteristics.

It is obvious that not all excipients or drugs would be directly compressible, that for such a system to work it would be necessary that some degree of “auto-compressibility” existed for *the major portion* of the ingredients (i.e., that they have fairly low-yield values).

The chapter to follow will deal with some of the directly compressible excipients that may be used for this purpose. Table 24.1 outlines the combination of properties that necessitate or allow the various processing options.

Table 24.1 Schematic for Process Selection

DC excipient concentration	Drug concentration	Drug flow rate	Drug compressibility	Method
Low	High	Good	Good	Direct compression
High	Low	Good or bad	Good or bad	Direct compression
		Bad	Good	Slugging, roller compaction
		Good	Bad	Wet granulation
		Bad	Bad	Wet granulation

24.2. LOADING AND PARTICLE SIZE CONSIDERATIONS

The following deals with mixtures of low concentrations of non-DC drugs with DC excipients. In some cases it is quite obvious (e.g., if one deals with a drug that is dispensed in microgram quantities) that the concentration is “low.” It is, in some situations, also obvious what *high* means (e.g., a sulfonamide [usually in doses of 250–500 mg]) would be a high concentration. The question is where the cutoff point is. A general rule of thumb (Carstensen, 1980), is that if the drug content is 16% or less, then direct compression is physically a possibility, even if the drug substance itself is not autocompressible. The experienced formulator, however, knows that trial-and-error is the only deciding factor. As Kirchhoff once said: “Theory guideth, experiment decideth.”

The 16%-rule (Carstensen, 1980) was arrived at on statistical grounds, the argument being that if a certain number of drug particles would find themselves as neighbors (as calculated by probability statistics) in a compact, then that would constitute a weak area in the tablet which could give rise to capping and breaking.

Another consideration, is that when the drug is present in higher concentration, then the DC component should be sufficient to “cover” the drug substance and, even more importantly, in the opposite case, the amount of drug should be enough to just cover the excipient. This is akin to ordered mixing.

This is particularly true in attaining adequate *blending and content uniformity*. To achieve ordered mixing the maximum amount of material of the “small size” component (in this case the drug) is given by the following argument (refer to Table 24.1). Consider the surface of the large particle (A_L); it can accommodate a certain number of small particles. Given the diameter of these, it is possible to calculate the number of small particles necessary to cover the large particle, and arrive at a critical weight ratio. However, it is usually difficult to assess particle size distributions of small particles (of particle diameter d), and it is easier to do as done by Nyström and Glazer (1985) and Nyström et al. (1982). These authors simply note that the projected area (the cross section) of the small particle is $\pi d^2/4$, which is the cross-sectional area of the small particle. This, in turn, equals one-fourth of the surface area of the small particle (Fig. 24.1).

The following nomenclature is now used: the number of small particles per large particle required for “full coverage” is n , the density of the small particle is ρ_S , and for the large sphere the diameter is D and the density is ρ_L .

The surface area of the large particle is

$$A_L = \pi D^2 \quad (24.1)$$

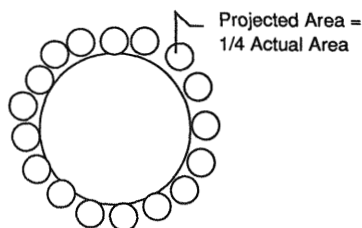


Fig. 24.1 Saturation point of small particles with large ones.

and the surface area of the smaller particles is

$$A_S = n\pi d^2 \quad (24.2)$$

The projected surface area (the cross section) is one quarter of this,

$$A_{\text{proj}} = A_S/4 = n\pi d^2/4 \quad (24.3)$$

so that the amount of material required to “fill up” the surface of the large particles is four times the surface area times the number of the small particles (i.e., $n4A_s$). The number of small particles n that will accommodate it is

$$n = A_L/\{A_s/4\} = \pi D^2/\{\pi d^2/4\} \quad (24.4)$$

The mass w_L of the large particle is:

$$w_L = \rho_L \pi D^3/6 \quad (24.5)$$

and the mass of small particles required to fill up the surface of the large particle is

$$w_1 = 4\{n\rho_s\pi d^3/6\} \quad (24.6)$$

The weight ratio W at complete coverage is, therefore

$$W = w_1/w_L = 4n\rho_s d^3/\rho_L D^3 = \{4A_s\rho_s d\}/\{A_L\rho_L D\} \quad (24.7)$$

where Eqs. (24.2) and (24.1) have been used in the last step.

For the large particle the specific surface area S_2 is given by

$$S_2 = \pi D^2/\{\rho_L \pi D^3/6\} = 6\rho_L/D \quad (24.8)$$

and similarly for the small particles

$$S_1 = 6\rho_s/d \quad (24.9)$$

Hence, the ratio R between the small and the large specific surface area is

$$R = \rho_s D/\rho_L d \quad (24.10)$$

and introducing this into Eq. (24.7) now gives

$$W = 4RA_s/A_L \quad (24.11)$$

The advantages of direct compression is primarily economic, but there are also disadvantages to direct compression. When drug concentrations are low, direct compression is a distinct possibility for a drug candidate. However, the hydrophobicity of the drug may be such that wetting is poor in the direct compression formulation. This may make a wet granulation a more desirable candidate for development because of dissolution and bioavailability considerations. However, there *are* cases for which the opposite is true.

The attainment of adequate content uniformity can be difficult, particularly when the drug content is low. Furthermore, direct compression can be dusty, and punch wear is considerably higher than for wet-granulated products.

24.3. DIRECT COMPRESSION MECHANISMS

It might be asked: “What physical characteristic of a substance makes it, or a mixture of it with other substances, directly compressible?” There are several possibilities for bonding mechanisms: (a) distance forces (van der Waals, hydrogen bonding, electrostatic forces); (b) solid bridging; and (c) mechanical interlocking. It should also be mentioned that asperite melting is, at times, possible.

In case (a) i.e., van der Waals forces (Carstensen, 1980), it is a matter of placing surfaces together at molecular distances. As shown in Fig. 24.2 this can happen (situation A) when asperites meet either other asperites or plane surfaces, or (situation B) when plane surfaces approximate within molecular distances, whereas (situation C) when two different substances “meet,” they may or may not bond, depending on the molecular arrangement.

Suffice it to say that (a) adsorbed air must somehow be “removed” to allow the surfaces to come in close contact, and (b) even when they come in contact, it is not a fusion in which there is total bonding (i.e., one is not making one crystal out of two crystals). But there are sporadic, or periodic, situations during which two phillip molecules come within molecular distances of one another and form a type of chemical bond. This type of bonding is the primary type for pharmaceutical materials (Nyström et al., 1993).

Bridging is a possibility as well, and has been reported (Olsson et al., 1996; Adolfsson et al., 1997).

In interlocking (Führer, 1977), large shape factors (irregular surfaces) and fractal dimensions (surface roughness) are the main contributors, as with microcrystalline cellulose (Nyström et al., 1993).

The point of asperite bonding was a favorite theory for a while (Rankell and Higuchi, 1968), then fell in disrepute, but obviously has some merit.

24.4. ASPERITE MELTING

With waxes, for instance, melting is the method by which bonding occurs. The same may hold for drug substances with low melting points (Skotnicky, 1953; Rankell and Higuchi, 1968).

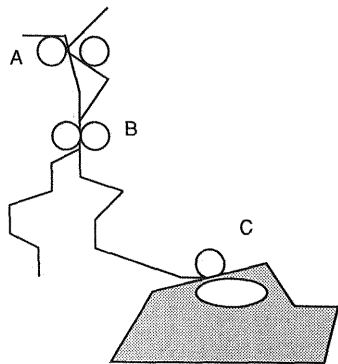


Fig. 24.2 Schematic of bonding by van der Waals forces.

Consider the situation in Fig. 24.3, in which a particle of A touches a particle of B. A and B can form eutectics and the shaded area then may become a eutectic mixture if the temperature at the particular surface point during compression is above the eutectic temperature. There have been several reports in the literature in which an overall increase in temperature during tableting has been demonstrated. At times, this has been done by simply measuring, calorimetrically, the temperature of the tablet mass as the tablets come off the machine, but the local temperature rise at contact points may be much higher.

If one simply considers the melting temperature T of a substance, it changes with pressure P and follows the Claperyron equation:

$$dT/dP = (V_L - V_S)T/\Delta H \quad (24.12)$$

where V_L is the molar volume of the melt, V_S is the molar volume of the solid, H is enthalpy of fusion.

For most substances $V_L > V_S$ so that the melting point *increases* with increasing pressure. (Water and bismuth are exceptions to this statement). So, although the temperature rises during compression, the pressure is such that the melting point is also expected to increase. Although this speaks against asperite bonding, the point has never been made that the question is really whether the eutectic temperature increases with increasing pressure.

Add to this the following argument: Stotnick (1953) and Rankell and Higuchi (1968), used thermodynamic and mechanical arguments, to show that *under stress* (as the particle is during compression), dT/dP will *always* be positive. Under those conditions the solid is under a pressure P_s , but the melt (liquid) is subjected to the atmospheric pressure in the void space, and in that case

$$dT/dP = V_S T/\Delta H \quad (24.13)$$

For instance, Stotnick (1953) demonstrated that under point pressure, naphthalene had a lowered-melting point, whereas it would normally would have a higher-melting point if both liquid and solid were exposed to increased pressure. Most solids would have a value of $dT/dP = V_S T/\Delta H$ of $0.2^\circ/\text{atm}$, so that, in general, asperite melting would not be suspected of compounds having high-melting points. Again, it is actually the eutectic temperature that is of importance.

Rankell and Higuchi (1968) employed an expression arrived at by Carslaw and Jaeger (1959) and found that for sulfathiazole

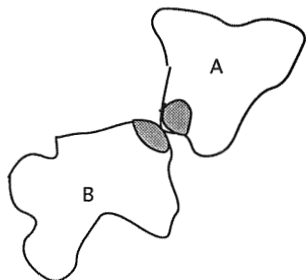


Fig. 24.3 Schematic of asperite bonding.

$$\Delta T = 0.046/f \quad (24.14)$$

where f denotes the fraction of the total area that is in actual contact. If this is 10^{-3} to 3×10^{-4} , then $\Delta T = 45\text{--}150^\circ\text{C}$, lending feasibility of asperite melting.

Again, the foregoing considerations apply to pure substances, and the possibility of eutectic formation can make asperite melting possible in mixtures, whereas it might not be feasible for the compound itself.

Asperite melting is generally not seriously considered as a mode of bonding in modern literature, although there are reports from time to time of its occurring and, however improbable, it should never be ruled out as a possibility.

24.5. VARIABLES

There are a host of variables that may affect the tableting performance of a direct compression formulation.

The *particle sizes* of both drug substance and direct compression excipient are of importance (see Fig. 24.1). As seen, when a drug substance is not autocompressible, there is a maximum load that the direct compression excipient can accommodate to make good tableting possible.

Milling (Adolphsson et al., 1998) has an effect transcending the particle size effect, because it affects the nature of the surface. Figure 24.4 shows the effect of milling of NaCl on the tensile strength of the resulting compacts.

24.6. DIRECT COMPRESSION EXCIPIENTS

The most commonly used direct compression excipients are

Spray-dried lactose
Dicalcium phosphate anhydrous (A-tab)
Dicalcium phosphate dihydrate (Di-tab)
Microcrystalline cellulose (Avicel; MMC)
Pregelatinized starch

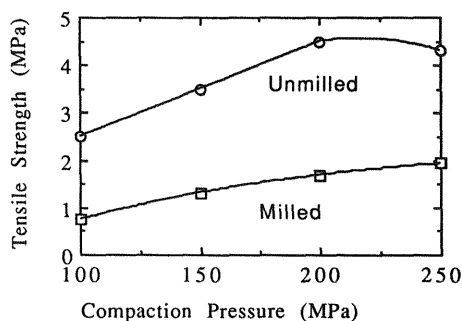


Fig. 24.4 Effect of milling on tensile strength. Least-squares fit: squares, milled: $y = -2.8 + 6.55 \cdot 10^{-2}x - 1.5 \cdot 10^{-4}x^2$; $R^2 = 0.995$; and circles, unground NaCl; least squares fit: $y = -0.3 + 1.3 \cdot 10^{-2}x - 2 \cdot 10^{-5}x^2$. (Data from Adolphsson et al., 1998.)

24.6.1. Microcrystalline Cellulose

MCC is a useful filler considered, in fact, by many technologists the best of direct compression excipients. However, it has limitations (Bolhuis and Chowhan, 1996); for instance the bulk density is low, it is sensitive to lubricants and lubricant level, it does not exhibit excellent flow, and its compression characteristics are somewhat dependent on moisture content. For the purpose of flow improvement, Tobyn et al. (1998) have investigated the common practice of adding pyrogenic silica as a glidant to the MCC. There are definite advantages to silicifying MCC, but Tobyn et al. (1998) found that this is not due to physiochemical changes (i.e., no bulk chemical change and no morphological change were observed). The mean aerodynamic diameter (obtained by means of an Aerosizer Mach 2) shifted from about 55 to 30 μm . If measured by Malvern Mastersizer, it changed from 122 to 105 μm , and the particle density (obtained by helium pycnometry) was unaltered. Flow rates were not reported, but it is generally known that silicized MCC flows more readily than plain MCC.

Malamartaris et al. (1984) have reported on the plastoelasticity and tableting of microcrystalline cellulose (in combination with acetaminophen (paracetamol)).

24.6.2. Maltodextrins

There are direct compression excipients other than the ones listed in the foregoing that have been reported in the literature. Mollan and Celik (1993, 1994, 1995) have shown that there are five types of maltodextrins and reported on the effect of storage and humidity on their direct compression quality. Velasco (1997) has reported the use of maltodextrins (Maltrin M510, Grain Processing Corporation, Muscatine, Iowa). Maltodextrins are glucose polymers that are water-soluble. They are produced by wet acid or enzymatic interaction with starch. Li and Peck (1990a,b) have reported them as wet granulation excipients, and Papadimitriou et al. (1992) as DC excipients.

24.6.3. Chitosan and Xylitol

There are yet other DC excipients that have been reported. Nagai et al., (1984) and Upadrashta et al., (1992) have found chitosan to be an excellent direct compression excipient.

Other DC excipients than the one mentioned in the foregoing exist and have been reported on. Joyce et al. (1997) have reported on the use of Xylitab 200* which is xylitol granulated with 2% sodium carboxymethyl cellulose.

Aside from the actual flow and compression requirements, direct compression excipients must also be able to perform under high-speed-tableting conditions. This has been investigated in several cases. Armstrong and Palfrey (1989), for example, have reported on the effect of machine speed on the performance of four DC excipients.

24.7. DRY BINDERS

At times the mere mixing of directly compressible substance does not suffice to make a product that is satisfactory in all respects. Olsson et al. (1998) point out that during

compression, particles are made to come in closer contact, and the porosity of the powder bed is thereby reduced. This is the primary cause of bond formation, resulting in a compact with a certain tensile strength.

If the strength of the tablet is less than desired, then an increase in tensile strength can be brought about by adding a binder before compression, and here, the binder is referred to as a *dry binder*. These are often ductile materials (e.g., polymers, such as derivatives of cellulose and starch).

Dry binders usually deform plastically and bond to the drug (and other) particles during compression, thus binding them together. The amount of dry binder must be enough to cover all or a substantial part of the surfaces of the remaining ingredients (Nyström et al. 1982; Nyström and Glazer, 1985; Adolphsson et al., 1998), and this amount, as shown earlier, is given by the relation

$$R_s = A_{\text{binder}} / \{4A_{\text{carrier}}\} \quad (24.15)$$

where A denotes weight-specific surface area, and R_s is the actual surface area ratio between binder and carrier.

Dry binders and their properties have been studied, such as their propensity to fragment, and the mechanism of their bonding (Nyström et al., 1982; Duberg and Nyström, 1985; Nyström and Glazer, 1985; Yu et al., 1989).

Olsson et al. (1998) have evaluated *polyoxyethylene glycols* (PEGs) of a range of molecular weights as dry binders. These compounds have been used as dry binders in direct compression; for instance, in combination with dicalcium phosphate (Larhrib et al., 1997; Larhrib and Wells, 1997a,b). The cooling rate from which PEG is made from a melt affects the morphology (Chatham, 1985; Craig and Newton, 1991; Larhrib et al., 1977b) so that the history of the PEG is of importance in such an application. Tensile strengths, however, may also be affected by rugosity and particle shape (Larhrib and Wells, 1997a,b).

24.8. MIXED DIRECT COMPRESSION EXCIPIENTS

When two materials are blended, they often improve compressibility and reduce propensities for lamination and capping of drugs with high-yield values. Tablets of mixtures exhibiting tensile strengths higher than tablets made from the individual components themselves may result, and Wells and Langridge (1981), for instance, have studied the dicalcium phosphate–microcrystalline cellulose system as a direct compression component. In this case the mixtures give harder tablets than those made from the component excipients (Vromans and Lerk, 1988; Newton et al., 1977).

Bi et al. (1999) have shown how the combination of Tablettose and microcrystalline cellulose as direct compression excipients and cross-linked sodium carboxymethyl cellulose (Ac-di-sol) as disintegrant allows optimization of directly compressed tablets.

24.9. EFFECT OF MOISTURE

Moisture may be expected to have an effect on direct (and other types of) compression. Moisture in small amounts can act as a lubricant. Furthermore, it facilitates the approach of particles to one another, so that particle-to-particle contact (without

interfacing air) is made easier. Large amounts of moisture are undesirable when direct compression is carried out because a drug substance may be moisture-sensitive (as, e.g., aspirin), or as in effervescent tablets when more than minimum amounts of water will cause reaction between acid and base on storage.

Nokhodchi et al. (1995a,b) have reported on the effect of moisture content on the compression and energy aspects of ibuprofen compaction.

Chowhan and Chow (1981a) studied the effect of water on methylcellulose granules. Granules made by wet granulations were slightly more compressible than directly compressible mixtures when the compression pressures were low, but at higher pressures the opposite was true. This became less pronounced at higher-moisture contents.

24.10. WET-GRANULATED TABLETS

This process was reviewed in Chap. 21. Historically, the oldest binder employed is probably cornstarch, which is made into a paste (e.g., in a 1:10 ratio) with water. One-tenth of it is suspended in one part of cold water, and added to nine parts of boiling water. This produces a paste that “glues” the drug and other excipient particles together. The wet mass is sized through a desirable size screen, dried, milled, lubricated, and compressed. The process is one of (a) *particle enlargement*, (b) improvement of the *roundness* of the particles, and (c) adding a *binder*. The two former properties, as mentioned in Chap. 21, aid in powder flow, and the latter aids in compressibility of the blend.

24.11. DEFECTS IN DIRECT COMPRESSION

At times anhydrous compression is dictated by the stability of a drug substance. Loading has already been discussed, but it is apparent that, if only small amounts of drug substance are present, then the finished tablet will have the properties of the direct compression ingredient. Defects will occur, and the most often encountered ones are discussed in the following.

The most common defect in direct compression is content uniformity. The aspects of this has been covered in Chap. 20.

It is difficult to compare directly compressible versus wet-granulated tablets. An ideally formulated wet-granulated tablet will not contain the same ingredients as a directly compressed tablet, but it is possible to compare tablets made from direct compression components that contain pregelatinized starch, prepared both dry and “wet.” It is true that the latter would have better-wetting properties, but it may not always be that important. The manner in which the magnitude of the effect may be investigated is to carry out dissolution studies on both tablets and uncompressed powder. If the uncompressed powder exhibits a lag time and the wet processed one none (or a much smaller lag time), then the wetting of the material, indeed, is of importance. This may not be sufficient to warrant *not* using a direct compression approach. Cost considerations may outweigh small differences in dissolution rates.

Many drug substances are very hydrophobic and have a very high-yield value, and in such cases, the presence of drug may give rise to capped tablets. If one considers the drug substance completely “incompressible,” then the tablet, when made, must not contain long “strings” of the drug substance. Suppose the tablet

is considered as a body-centered cubic array, then there will be six points of contact, and the probability of a drug particle being one of these is equal to the fraction f of drug in the tablet. The probability that two drug particles should be neighbors is $6f$. The probability of having a row of three would be $(6f)^2$, and so on, so that if there are n particles in a row, then the probability is $(6f)^{n-1}$. If the presence of n particles in a row is sufficient to cause a defect, then n is given by this number. It is possible, therefore, to calculate the percentage of defects to be expected as a function of f and n . This is shown in Table 24.2.

24.12. SLUGGING AND ROLLER COMPACTION

There are high-dose drug substances that, of necessity, are present in their formulas in a high concentration (e.g., aspirin). If the drug is of reasonable yield value (is compressible), but flows poorly, then one often resorts to slugging or roller compaction.

In slugging, large tablets (e.g., 2-in. diameter) are made using very heavy-duty machines, so that the adequate slugging pressure (force divided by area) can be achieved. These tablets may not have good fill weight uniformity, but this does not matter, because they are broken up in the next step by coarse milling. This has as its goal to make particles that are larger and, one hopes, rounder, than the original powder. These then flow well and can be compressed directly on a tablet machine to the correct dimensions and with adequate weight control.

A more convenient way of doing this is roller compaction (Fig. 24.5). In this process, two rollers, with high pressure applied between their centers, are rotated, and the powder is processed through them and exits as a compacted sheet, which can then be broken up and tableted directly.

The powder is fed into the space ABCD in Fig. 24.5, where it attains its cascaded apparent density ρ' . The powder is forced downward into the region CDEF by gravity and the weight of the powder above it (and in some equipment by force feed). Rearrangement of particles makes the powder attain its tapped density ρ'_{tap} in the space CDEF.

Friction (or force-feeding) now carries the particles down into the area EFGH, where they are compacted into a sheet, which feeds out below the area GH.

Table 24.2 Percentage of Defects Expected in Direct Compression for Different Numbers of n^a and x (see text)

100× (%)	% defects when $n = 3$	% defects when $n = 5$	% defects when $n = 10$	% defects when $n = 20$
8	25	5	0.1	
10	35	15	1	
13	60	35	10	1
15	80	65	40	15

^a n is the number of neighboring drug particles needed to produce a defect.

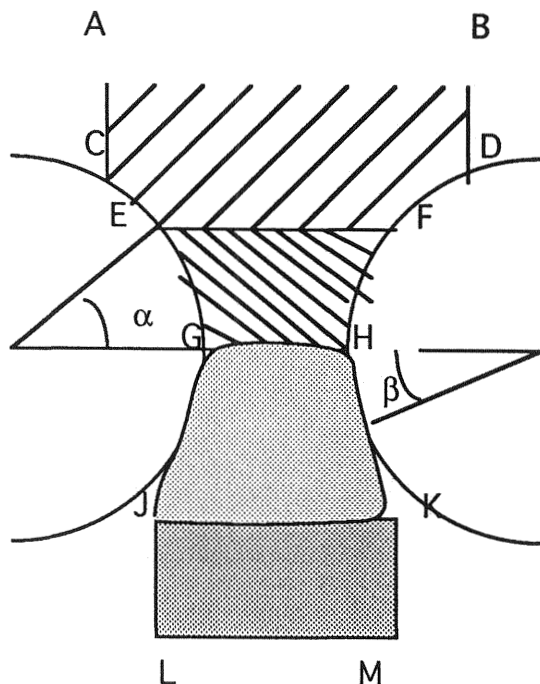


Fig. 24.5 Schematic of a double-roll compactor.

The angle α is denoted the gripping angle, the angle of rolling, or the angle of compaction. In the zone of compaction, EFGH, there is a pressing force, and some deformation of particles, followed by plastic deformation, or brittle fracture occurs. The sheet itself will usually be thicker than its exit thickness GH, because of elastic recovery of the compacted mass. The angle where this final thickness is achieved is called the angle of release, β .

The work reported in literature is phenomenological in nature, and an all-inclusive theory of roller compaction has not yet appeared (Pietsch, 1990).

24.13. HARDNESS (CRUSHING STRENGTH, TENSILE STRENGTH)

Hardness is measured by placing a tablet between two anvils and measuring the force (most often recorded in kilopond) required to break it (e.g., a Schleuniger Hardness Tester). When the force is divided by the area over which the force acts (the rectangular, cross-sectional area of the tablet; Fig. 24.6), it is referred to as the yield stress of the tablet.

A tablet, when first made, may possess a certain hardness, but this may change with time, often quite rapidly, and then level off at an equilibrium value.

The magnitude of the hardness change is related to the type and concentration of binder used in wet granulation. Chowhan and Palagyi (1978) studied wet granulations of naproxen (e.g., with hydroxypropyl methylcellulose [HPMC] and other granulating agents) with particular emphasis on the effect of moisture on "stability" of hardness. They proposed that compression exudes water from the granulation

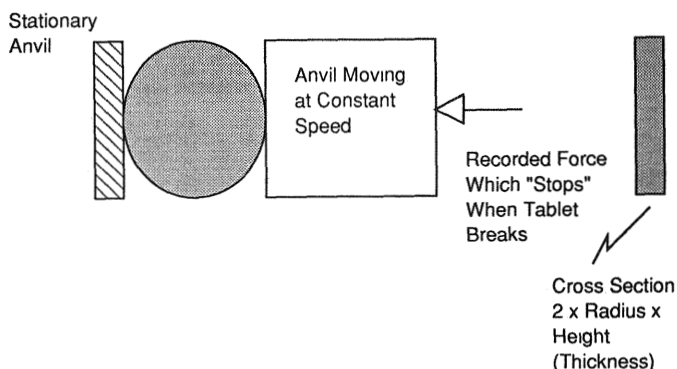


Fig. 24.6 Schematic of a diametral hardness test.

into the void space, and that this causes recrystallization of the drug or soluble excipients. This (as opposed to hardness-induced decrease, not attributable to moisture loss, of dissolution) does not affect dissolution.

Chowhan (1980) has used HPMC in salicylic acid tablets. Tablets at different moisture levels increase in hardness on standing overnight. He found this loss to be linearly related to the amount of moisture lost under compression. The moisture-induced hardness increases in tablets prepared from granulations containing different binders, but they had no effect on the tablet disintegration time and in vitro drug dissolution.

Stubberud et al. (1996) and Sebhatu et al. (1994) observed increased tablet-crushing strength during storage, and attributed this to a reduction in the glass transition temperature (T_g), induced by moisture, eventually giving rise to crystallization. This, in turn, increased bonding strength by way of solid bridge formation. Stubberud and Forbes (1998) found that polyvinyl pyrrolidone (PVP) would delay the recrystallization, but that hydrophobic excipients would accelerate it.

The aspects of tablet hardness and crushing strength for wet-granulated tablets is approximately the same, from a mechanical point of view, as that for directly compressed tablets.

Krycer et al. (1983a,b) have studied the crushing strength versus lower punch work and reported on tablet characteristics of tablets made by wet granulation (dissolving HPMC to 8% w/w water, with a total HPMC concentration of 3% w/w).

Tablet hardness is a function of the magnitude of the pressure that has been employed to make it. Figure 24.7 shows this type of plot, often referred to as a *compression profile*. Typically (particularly in company literature showing the virtues of a particular direct compression ingredient), these are plotted in linear fashion (i.e., up to point A in Fig. 24.7), but the fact of the matter is that they are always somewhat curved. If the point B occurs at a higher than achievable compression force, then linearity is fairly good.

24.14. CAPPING

The reason for the parabolic nature of the plot (see point B in Fig. 24.7) is that the tablet will start laminating and capping at high pressures, and this gives rise to a

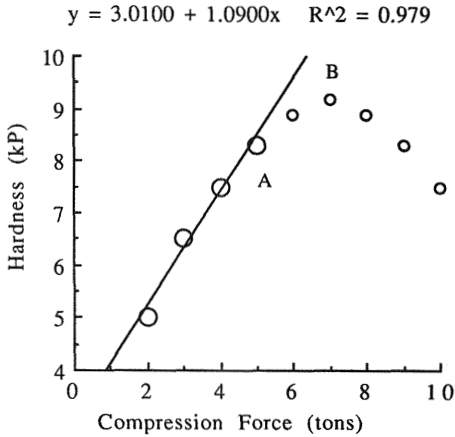


Fig. 24.7 Compression profile: The section AB is what is most often shown in publications. It is almost linear. When materials are poorly compressible, then curvature occurs at lower pressure values.

weaker tablet (i.e., the hardness will decrease). Capped and laminated tablets are shown in Fig. 24.8.

The reasons for the occurrence of cappers is that after the upper punch has reached its maximum pressure and starts retracting, the stress is released *uniaxially* (i.e., the tablet expands in only one direction). This gives rise to decompressional stress on the tablet. A high-compression pressure would give rise to a large number N , of contact points (i.e., many bonds are formed). At a given point, however, the extra strength imparted by additional pressure is offset by the additional stress in the expansion.

Hiestand has proposed indices that are directly measurable for determining the propensity for capping.

24.15. UNIAXIAL EXPANSION

In compression, several bonds, N_f , are created, and this number is proportional to the compression pressure, so that doubling the pressure would cause a doubling in the number; that is,

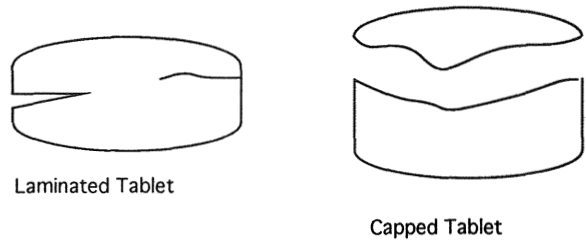


Fig. 24.8 Laminated and capped tablets.

$$N_f = \beta P \tag{24.16}$$

The return of the upper punch causes a number of bonds N_d to be destroyed, and this number will often be proportional to P to a power (e.g., to P^2).

$$N_d = \phi P^2 \tag{24.17}$$

The total number of surviving bonds after ejection will be

$$N = N_f - N_d = \beta P - \phi P^2 \tag{24.18}$$

and the hardness would be proportional to this number. The hardness, therefore, is a function of applied force by a parabolic (or other power) relation with a maximum at point B where

$$dN/dP = 0 = \beta - \phi P, \quad \text{i.e. } P = \beta/\phi \tag{24.19}$$

as depicted in Fig. 24.7.

24.16. BONDING TYPES

There are three different types of bonding: (a) Weak forces, e.g., van der Waals forces; electrostatic forces, and hydrogen bonding (distance forces); (b) The second type is mechanical interlocking (Führer, 1977); and (c) the third is solid bridges.

Adolphson et al. (1998) have shown (for the case of sodium chloride) that milling of the particles, or adding a dry binder, reduces the significance of solid-bridge bonding, but increases the importance of weak distance forces. The effect is shown in Fig. 24.4. It is noted that the tensile strength is higher for the ground NaCl, but that the critical capping pressure is less.

If Heckel plots are carried out for two different mesh cuts of a solid, then, if the bonding is by brittle fracture, the initial compression will crush particles and, as the

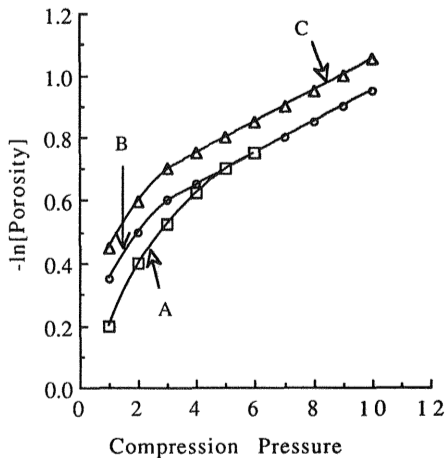


Fig. 24.9 Athy–Heckel plots of a fine-mesh fraction of a substance (A) fracturing by brittle fracture; (B) plot of a coarser fraction of the same substance. Athy–Heckel plots of a fine-mesh fraction (B) fracturing by plastic deformation and (C) the same plot of a coarser fraction of the same compound.

pressure is increased, the behavioral difference between the two fractions will disappear (shown in Fig. 24.9 as comparison between A and B).

If, on the other hand, the substance bonds primarily by plastic deformation, then the coarse fraction (now C) will become parallel with the fine fraction (now B).

If bonding is by brittle fracture, then fairly large amounts of lubricants (e.g., magnesium stearate) may be incorporated without sizable influence on tablet hardness (e.g., dicalcium phosphate dihydrate), whereas a substance bonding by plastic deformation (e.g., hydroxyapatite), will fail to form tablets *at all* above a certain, fairly low (e.g. 1.5%) concentration of magnesium stearate.

24.17. OPTIMIZATION

The area of statistical optimization of formulae is outside the scope of this book; however, some mention of the subject is in order. A fairly large body of literature has been written on the subject of optimization and pharmaceutical applications (Schwartz, 1996).

In practice, however, one must recognize that formulations are multicomponent systems; hence, they offer a great number of possibilities for interactions and, furthermore, complete factorials, as shall be seen, lead to excessive amounts of experiments. In general it is wise to have as few components as possible, but it is seen in the foregoing, that several functional ingredients are necessary:

- Drug substance (unless the formula is a placebo)
- Binder
- Disintegrant
- Lubricant
- Filler (to obtain the desired fill weight)
- Glidant (at times).

With as little as six ingredients, if one were to test high and low levels (and consider the filler the q.s. ingredient), then there would be five high (+) levels and five low (−) levels, so that the number of combinations would be $2^5 = 32$. If, furthermore, a midlevel were desired, then five zero levels would also be required, so that the number of preparations made for a “complete” factorial study would be 3^5 (i.e., 243). This is obviously an excessive amount and, furthermore, other variables are of importance (e.g., what is the effect of different lots of each raw material?).

It is conventional with some investigators to do *screening* first (i.e., fix the ingredients that will be used in the formula and then optimize the amounts). This is a classic mathematical and search method.

The second method is to do optimization while the experimentation is ongoing, and two methods are used for this, the evolutionary operations (EVOP) and the simplex method.

The first method is facilitated by knowing a (at least phenomenological) relation (equation) connecting responses (disintegration, hardness) to variables (amounts, compression pressure).

With an *incomplete* factorial, however, some combination of methods is possible. Rather than testing three levels in a complete factorial, one might test more in an incomplete factorial. If, as in the example, there are five independent variables x_i ,

then the response, y (e.g., hardness, percentage coppers, dissolution half-life) may be fitted to a polynomial of the form:

$$y = a + \sum \{bx_i + cx_i^2\} \quad (24.20)$$

Three experiments for each variable, in this case a total of 15 experiments will give “first” values of a_i , b_i , and c_i so that the parameters (y) may be maximized. More values than 15 may be used, and this will (a) make precision better and (b) permit testing for interactions.

What is not, usually, treated in exacting optimization procedures is the following: Several properties (responses) are tested for, and they will each optimize at different values of the variables. The question, then, is to decide which of the parameters are most important. These could be, for instance, hardness and dissolution. Often dissolution decreases with increasing hardness, so that optimum dissolution might occur at hardnesses that are not acceptable. In this case, then, statistics are actually abandoned, and a decision is made to accept a formula that is optimum for neither hardness nor dissolution, but acceptable for both.

Once one has arrived at the formula, then a EVOP method (Box et al., 1978) may be used to further optimize the composition. In this one “triangulates” a further experimental scheme (Fig. 24.10).

In Fig. 24.10, the experimentation is started with a percentage of lactose corresponding to A, and experiments are made in three directions. It is noted that the direction AB gives an improvement, whereas the other two directions do not. The next set of experiments is then started at B in three “directions,” and it is seen that going to C gives a better (and the best result). The next set of experiments now start at C, but all give results inferior to the composition at C, so that C is deemed to be a local maximum.

The amount of lactose that optimizes hardness may not optimize dissolution rates.

Other methods have been published. Bi et al. (1999) have described a procedure for which all factors have been combined in multiple regression plots to obtain ranges of variables giving the best tablet.

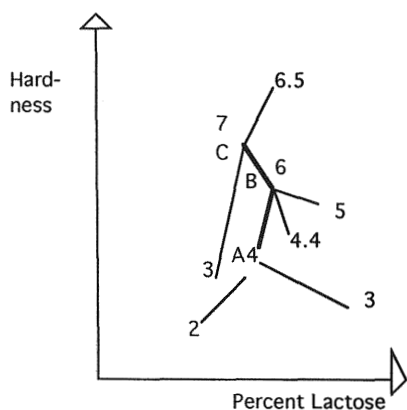


Fig. 24.10 Example of attainment of optimum conditions in a tablet formulation.

SYMBOLS

- A = (a) surface area; (b) cross-sectional area of tablet
 A_L = surface area of a large particle
 A_S = surface area of the smaller particles
 A_{proj} = projected surface area (the cross section) of a small particle
 a = constant in the (a) Heckel; (b) Cooper–Eaton equation
 b = constant in the (a) Heckel; (b) Cooper–Eaton equation
 c = specific heat
 D = (a) diameter of a large sphere; (b) dose
 d = diameter of small spheres adhering onto a larger sphere
 f = fraction of the total area of two particles that is in actual contact.
 ΔH = heat of fusion
 h = thickness of tablet
 N = number of contact points in compression
 N_d = number of bonds broken during decompression
 N_f = number of bonds formed
 n = the number for “full coverage” of a large particle by small particles
 q = heat transfer rate
 P = pressure
 $P(1)$ = pressure at which deformation is reversible
 $P(2)$ = pressure at which deformation is irreversible
 $P(3)$ = pressures at which plastic deformation or brittle fracture occurs
 R_s = actual surface area ratio between binder and carrier
 R = ratio between the specific surface areas of small and the large particles
 S_2 = specific surface area of large particle
 S_1 = specific surface area of small particle
 T = melting point
 t = length of time of heating
 V_L = molar volume of a melt
 V_S = molar volume of a solid
 $W = w_1/w_L$ = (a) weight ratio at complete coverage of large particle by small particles; (b) W = flow rate
 w_L = mass of a large particle
 w_1 = mass of small particles required to fill up the surface of the large particle
 x_i = composition variable of the i th component (e.g., amount of lactose)
 y = response variable (e.g., hardness)
 α = the gripping angle in roller compaction
 β = (a) angle of release in roller compaction; (b) proportionality factor between pressure and number of bonds
 ϕ = factor to P^2 to describe number of bonds
 ν = Poisson’s ratio
 ρ = particle density
 ρ_S = density of small particles
 ρ_L = density of a large sphere

REFERENCES

- Adolfson Å, Caramalla C, Nyström C (1998). *Int J Pharm* 160:187.
- Armstrong NA, Palfrey LP (1989). *J Pharm Pharmacol* 41:149.
- Bi YX, Sunada H, Yonezawa Y, Danjo K (1999). *Drug Dev Ind Pharm* 25:571.
- Bolhuis CK, Chowham ZT (1996). In: Alderborn G, Nyström C, eds. *Materials for Direct Compression*. Marcel Dekker, New York, pp 419–501.
- Duberg M, Nyström C (1985). *Int J Pharm Technol Prod Manuf* 6:17.
- Carlslaw HS, Jaeger JC (1959). *Conduction of Heat in Solids*. Oxford University Press, London, p 75.
- Carstensen JT (1980). *Solid Pharmaceutics: Mechanical Properties and Rate Phenomena*. Academic Press, New York, p 170.
- Chatham SM (1985). Characterization of molten filled hard gelatin capsules. PhD dissertation, Department of Pharmacy, Chelsea College, University of London.
- Chowhan ZT (1980). *J Pharm Sci* 69:1.
- Chowhan ZT, Chow YP (1981). *J Pharm Sci* 70:1134.
- Chowhan ZT, Palagyi L (1978). *J Pharm Sci* 67:1335.
- Duberg M, Nyström C (1986). *Powder Technol* 46:67.
- Führer C (1977). *Labo-Pharm Prob Technol* 25:759.
- Joyce J, Cirunay N, Plaizier-Vercammen A (1997). *Drug Dev Ind Pharm* 23:245.
- Krycer I, Pope DG, Hersey JA (1983a). *Powder Technol* 53:3.
- Krycer I, Pope DG, Hersey JA (1983b). *Powder Technol* 34:39.
- Lahrib H, Wells JI (1997). *Int J Pharm* 153:51.
- Lahrib H, Wells JI, Rubinstein MH (1997a). *Int J Pharm* 147:199.
- Lahrib H, Wells JI, Rubinstein MH (1997b). *Int J Pharm* 147:187.
- Li LC, Peck GE (1990a). *Drug Dev Pharm* 16:1491.
- Li LC, Peck GE (1990b). *J. Pharm Pharmacol* 42:272.
- Malamataris S, Bin Baie S, Pilpel N (1984). *J Pharm Pharmacol* 36:616.
- Mollan MJ, Celik M (1993). *Drug Dev Ind Pharm* 19:2335.
- Mollan MJ, Celik M (1994). *Drug Dev Ind Pharm* 20:3131.
- Mollan MJ, Celik M (1995). *Int J Pharm* 114:23.
- Nagai T, Sawayanagi Y, Nambu N (1984). *Chitin, Chitosan, and Related Enzymes*. Academic Press, Orlando, FL, pp 21–39.
- Newton JM, Cook DT, Holleborn CE (1977). *J Pharm Pharmacol* 29:247.
- Nochodchi A, Rubinstein MH, Larhrib H, Buyot JC (1995a). *Int J Pharm* 118:191.
- Nochodchi A, Rubinstein MH, Larhrib H, Guyot JC (1995b). *Int J Pharm* 120:13.
- Nyström C, Glazer M (1985). *Int J Pharm* 23:255.
- Nyström C, Mazur J, Sjögren J (1982). *Int J Pharm* 10:209.
- Nyström C, Alderborn B, Duberg M, Carehill PG (1993). *Drug Dev Ind Pharm* 19:2143.
- Olsson H, Adolfsson Å, Nyström C (1996). *Int J Pharm* 143:233.
- Olsson H, Mattson S, Nyström C (1998). *Int J Pharm* 171:31.
- Papadimitriou E, Efentakis M, Choulis NH (1992). *Int J Pharm* 86:131.
- Pietsch WB (1970). In: Fayed ME, Otten L, eds. *Handbook of Powder Science and Technology*. Van Nostrand Reinhold, New York, pp 276–267.
- Poukavos N, Peck GE (1993). *Pharm Res* 10:13363.
- Rankell AS, Higuchi T (1968). *J Pharm Sci* 57:574.
- Sebhatu T, Elamin AA, Ahlneck C (1994). *Pharm Res* 11:1233.
- Sheen P, Kim S (1989). *Drug Dev Ind Pharm* 15:401.
- Stotnický J (1953). *Czech J Phys* 3:225.
- Stubberud L, Forbes RT (1998). *Int J Pharm* 163:145.
- Stubberud L, Arwidson HG, Larsson A, Graffner C (1996). *Int J Pharm* 134:179.
- Tobyn MJ, McCarthy BP, Staniforth JN, Edge S (1998). *Int J Pharm* 169:183.

- Upadrashta SM, Katikaneni PR, Nuessle NO (1992). *Drug Dev Ind Pharm* 18:1701.
- Van Kamp HV, Bolhuis GK, DeBoer AH, Lerk CF, Lie-a-huen L (1986). *Pharm Acta Helv* 61:221986.
- Velasco V, Munoz-Ruiz A, Mondero C, Jiménez-Castellanos R (1997). *Int J Pharm* 152:111.
- Vromans H, Lerk CF (1988). *Int J Pharm* 46:183.
- Wan LSC, Choong YL (1986). *Pharm Acta Helv* 61:150.
- Wells JI, Langridge JR (1981). *Int J Pharm Technol Prod Manuf* 2:1.
- Yu HCM, Rubinstein MH, Jackson IM, Elsabbagh HM (1989). *Drug Dev Ind Pharm* 15:801.

RECOMMENDED READING

- Alderborn G, Nyström C (1996). *Materials for Direct Compression*. Marcel Dekker, New York.

Disintegration and Dissolution

25.1. Disintegration	427
25.2. Tablet Disintegration Models	429
25.3. Force Models in Disintegration	431
25.4. Dissolution of Drugs from Tablets	432
25.5. Compression-Coated and Multiple-Layer Tablets	435
Symbols	436
References	437
Recommended Reading	438

Disintegration and dissolution are crucial properties of tablets. To this end, disintegrants are added to tablet formulations (and at times to hard-shell capsule formulas as well). There is often a direct correlation between disintegration times and dissolution rate constants (Carstensen et al., 1978, 1980a,b,c, 1995).

25.1. DISINTEGRATION

Tablets, when made, must (in most cases) disintegrate to afford acceptable dissolution rates. Disintegrants work by swelling and causing a high degree of stress on the tablet. This will be covered in more detail in this chapter. Disintegrants also allow formation of channels that allow water (or other liquid) permeation into the tablet. Common disintegrants are starch and modified starches. There are several other disintegrants for the formulator to choose from. Explotab, Ac-Di-Sol, Avicel PH101, and Avicel PH102 have been compared by Chebli and Cartilier (1998), who also investigated cross-linked cellulose (CLC), and an extract of their results is reconstructed in Table 25.1.

It is seen that Explotab^R and Ac-Di-Sol^R, the so-called superdisintegrants, are superior to the three other disintegrants. Avicels^R is listed (for instance in the

Table 25.1 Comparison of Disintegration Times of Direct Compression Tablets^a Containing Six Different Disintegrants at the 5% Level

Filler	CLC-C25	Explotab	Ac-Di-Sol	Avicel PH101	Avicel PH102
Emcompress ^b	15	15	7.4	266	> 1200
Lactose 100-mesh spray-dried	16.1	15.6	24.8	16	39.7
Lactose	460	142	75	> 1080	> 1200

^a The tablets contain 0.5% magnesium stearate.
^b Dicalcium phosphate dihydrate.

Handbook of Excipients, or in Lieberman et al., 1989) as a disintegrant, but its disintegrating power is much less than the others.

Basically, both Explotab^R, and Ac-Di-Sol^R give approximately the same disintegration times at 2 and 3% levels, so that using these at a 2% level generally suffices to obtain maximum disintegration efficiency.

Chebli and Cartilier (1998) have investigated a cross-linked cellulose (CLC) as disintegrant and compared it with Avicel PH101, Avicel PH102 (both microcrystalline celluloses), Ac-di-Sol, and Explotab.

The disintegrants work in that (a) they facilitate the penetration of liquid into the tablet (e.g., by reducing the contact angle; and (b) they swell on contact with water.

The reason spray-dried lactose is more “difficult” to make disintegrate is that it is more soluble (owing to its amorphicity) than crystalline lactose dihydrate. This causes the disintegrant to swell, but it has no solid planes on which to exert its force, and this slows down the disintegration.

Some investigators check the *swelling volume*. This is performed by centrifuging suspensions of the disintegrant in both water and in paraffin and, then, measuring the volumes of sedimentation V_w and V_p . The ratio V_w/V_p is denoted the *swelling capacity* (Chebli and Cartilier, 1998), and for microcrystalline celluloses (Avicels), it is approximately equal to unity. This means that the manner in which these disintegrants work is *not* by expansion, but simply, by aiding the filling of the void space with disintegrating liquid.

The *rate of water uptake* is also of importance (e.g., Van Kamp et al., 1986; Sheen and Kim, 1989; Poukavoos and Peck, 1993; Chebli and Cartilier, 1998). This is performed in an apparatus that consists of a glass-fritted disk filter that connects to a 2-mL pipette by way of tubing (e.g., Tygon). This assembly is arranged vertically. A tablet is positioned in contact with the fritted disk, so that water will draw into the tablet. The uptake is then recorded as a function of time as the water level in the pipette changes. The porosity of the tablet will affect the water-uptake rates (Wan and Choong, 1986). Results for the MCC samples and CLC (Chebli and Cartilier, 1998) are listed in Table 25.2.

Table 25.2 Rate of Water Uptake by Tablet as a Function of Time

Excipient	Swelling capacity $V_{\text{water}}/W_{\text{paraffin}}$	$10^3 \times$ initial uptake rate of water (mL/s)
Avicel PH101	0.95	5.9
Avicel PH102	0.95	1.8
CLC-C25	0.92	3.5

Source: Chebli and Cartilier, 1998.

25.2. TABLET DISINTEGRATION MODELS

Disintegration is a function of two factors: (a) first the disintegration medium (e.g., water) must penetrate the tablet; and (b) then the disintegrant must swell, and force the tablet apart. One additional factor is at work; namely, the wetting of the tablet, that is, the surface must first “wet” so the contact angle ϕ between the solid surface, and the liquid must be as small as possible.

Couvreur (1975) showed that unmodified cornstarch reduced the wetting angle, and aided the flow of liquid into the pore space. If one considers a tablet to be porous and to possess one pore radius r (the average; i.e., an approximation), then the rate of penetration of the liquid (Nogami et al., 1966; Couvreur, 1975) will be

$$dL/dt = Qr^2/8\eta L \tag{25.1}$$

where L is the length penetrated at time t , η is the viscosity of the disintegration medium, and Q is a constant given by

$$Q = (2\gamma \cos[\phi]/r) - g \rho \sin[\alpha] \tag{25.2}$$

where γ is interfacial tension, g is the gravitational acceleration, α is the angle between liquid and capillary wall, and ρ is the density of the liquid. Integration of Eq. (25.2) gives (Couvreur, 1975)

$$L^2 = \{r\gamma \cos[\phi]/2\eta\}t \tag{25.3}$$

where the last term in Eq. (25.2) has been dropped.

The effect of tableting pressure (Berry and Ridout, 1950) is such that (a) increased pressure decreases the pore size, so that penetration rate is lowered, but (b) too low a pressure will allow the pores to be so large that the disintegrant, when it swells, will not exert the desired pressure on the tablet. Hence, disintegration as a function of pressure (Berry and Ridout, 1950) will give rise to graphs of the type shown in Fig. 25.1.

The last part of this curve is often presented in sigma-minus functional form (Kennon and Swintosky, 1958) (Fig. 25.2; where the y -asymptote is assumed to be 21 units).

Most tablets swell and then disintegrate (Carstensen, 1976; Carstensen et al., 1978a,b,c). A first step in modeling would be to imagine a tablet simply disintegrating at constant volume into particles of the same size. This is not correct (Khan and

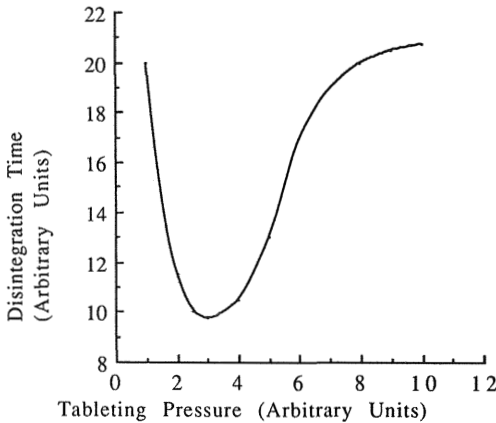


Fig. 25.1 Schematic figure of the effect of tableting pressure on disintegration time.

Rhodes, 1975), because the resulting particles have definite distributions, but with the simpler model, the mathematics to follow is sufficiently simplified to be tested.

In this view, one may assume that the tablet consists of T_0 particles, and that these simply “fall off,” and that happens semilogarithmically in time (i.e., the weight of the tablet is proportional to the number of nondisintegrated particles T , at time t , and the density of the granula)

$$T = T_0 e^{-qt} \tag{25.4}$$

where T_0 is the initial number of particles, and q is a rate constant. The weight (mass) M remaining at time t therefore, is given by

$$M = M_0 e^{-qt} \tag{25.5}$$

if the tablet is nonswelling. That this is correct for tablets that swell minimally was demonstrated experimentally by Carstensen et al. (1978a,b,c), as shown in Figs. 25.2 and 25.3.

A model by Kitamori and Shimamoto (1976) and Kitamori and Iga (1978) considers the number of particles N that have dislodged at time t by

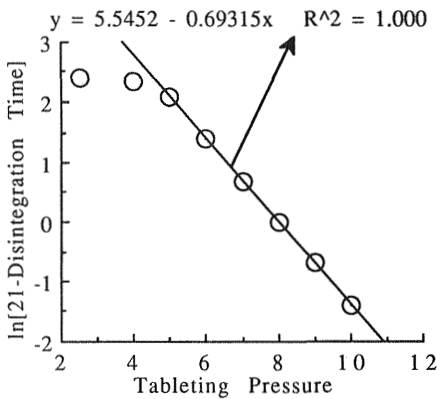


Fig. 25.2 Logarithmic presentation of the end data in Fig. 25.1

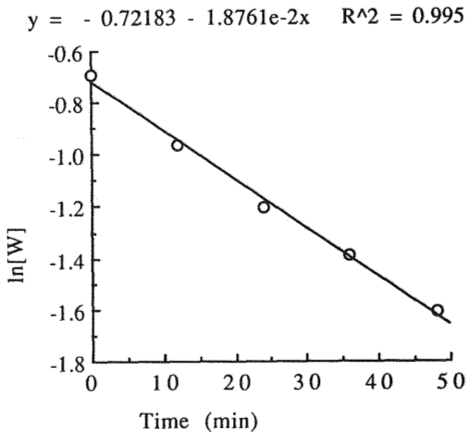


Fig. 25.3 Weight of a disintegrating tablet as a function of time represented semilogarithmically. (Data from Carstensen, 1978a,c.)

$$N = T_0/(t/t_g)^m \tag{25.6}$$

where t_g is disintegration time and m is a constant.

25.3. FORCE MODELS IN DISINTEGRATION

The previous section dealt with disintegration, and the scheme by which disintegration takes place, stepwise, is shown in Fig. 25.4.

- 1. First, the tablet has to wet,

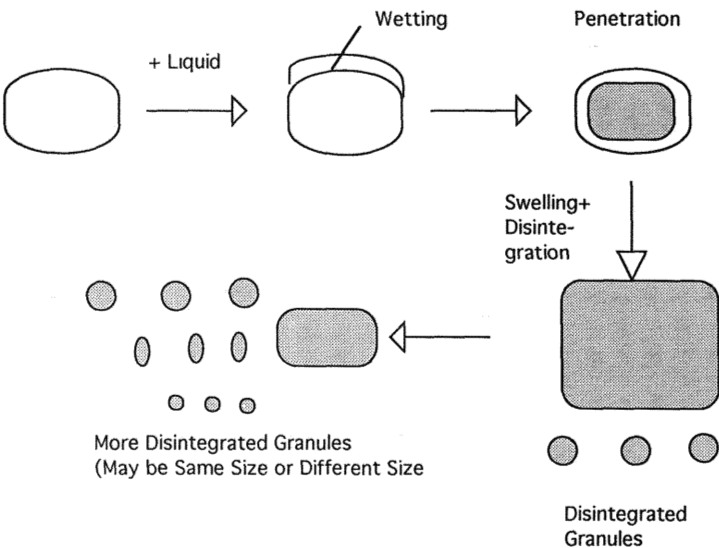


Fig. 25.4 Schematic of disintegration of a tablet.

2. Then, the liquid has to penetrate,
3. Then, the disintegrant swells and the volume (mass) of the tablet increases
4. Then, the tablet disintegrates

Several authors (Timmermans et al., 1995; Colombo et al., 1981, 1984; Catellani et al., 1989; Faroongsamg and Peck, 1994; Caramella et al., 1984, 1987) have described equipment with which it is possible to measure the pressure the tablet exerts on confining plates, and this force is proportional to its volume which, in turn, is proportional to its mass W .

The equation for the weight may be divided into

1. The weight of the dry (or dry part of the) tablet W_s , which decreases with a first-order rate constant of k_w
2. The weight of the adsorbed moisture W_w , which is associated with an absorption rate constant k_d
3. The weight of the dislodged granules W_d

The differential equations that this dictates are as follows:

$$dW_s/dt = -k_w W_s \quad (25.7)$$

$$dW_w/dt = k_w W_s - k_d W_d \quad (25.8)$$

$$dW_d/dt = k_d W_d \quad (25.9)$$

These equations are identical with the equations for an A–B–C reaction (Carstensen, 1978, 1995). The pressure exerted is proportional to the added weight, which would be W_w , and the solution for the Eq. (25.8) of the equation system is

$$W_w = \{k_w/(k_w - k_d)\} \{\exp(-k_s t) - \exp(-k_w t)\} \quad (25.10)$$

The pressure P is proportional to W_w , so that the curve for P versus time will have a maximum. Curve-fitting of the data will provide the values of k_s and k_d .

25.4. DISSOLUTION OF DRUGS FROM TABLETS

It is visualized that the tablet disintegrates by the foregoing equations, and it will be assumed in the following that the granules are all of the same size and that the diffusional release from the granule is given by

$$m_0 - m = m_0 \{1 - \exp(-kt)\} \quad (25.11)$$

where m is the mass of the individual granule at time t , k is the release rate constant, and m_0 is the mass of the particle as it is dislodged from the tablet. It is assumed that release occurs only from the granules, not from the tablet itself (which has a much smaller specific, external surface area). The amount of particles T released at a given time is given by

$$T = T_0 \{1 - \exp(-qt)\} \quad (25.12)$$

If a tablet starts disintegrating at time zero, then at time t the situation will be given as shown in Fig. 25.5.

The time element is divided into N intervals, and in the first interval has been “in existence” for t min from its “birth.” Hence, at this time, the number of particles

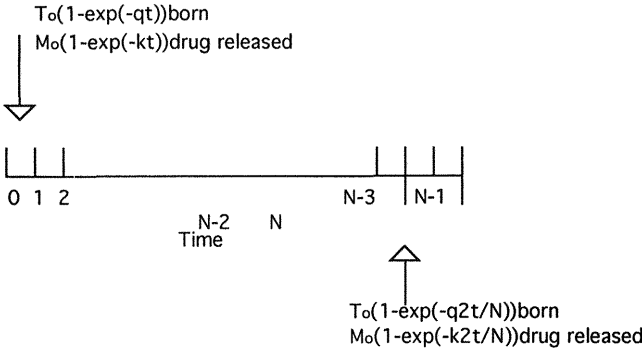


Fig. 25.5 Schematic for disintegration–dissolution event.

produced is $T_0(1 - \exp(qt))$. The amount of drug released from them is computed as follows:

The amounts released during the first two and the last two intervals would be the number of particles released in each interval (t_i) times the amount dissolved (m_i) at time t after they had been allowed to dissolve for t , $t - (t/N)$, $\dots(t - t(N - 1)/N)$ and $(t - tN/N)$ time units. The two last figures are t/N and zero. Hence,

Time of birth	Number of particles	Amount dissolved
0	$t_0\{1 - \exp(-qt)\}$	$m_0\{1 - \exp(-kt)\}$
1	$t_0\{1 - \exp[-qt(1 - 1/N)]\}$	$m_0[1 - \exp[-kt(1 - 1/N)]]$
...		
$N - 2$	$t_0\{1 - \exp[-qt(1 - (N - 2)/N)]\}$	$m_0[1 - \exp[-kt(1 - (N - 2)/N)]]$
$N - 1$	$t_0\{1 - \exp[-qt(1/N)]\}$	$m_0[1 - \exp[-kt(1/N)]]$

When these are summed, the total amount released is

$$\begin{aligned} M_0 - M &= \sum_{n=0}^N t_0\{1 - \exp[-qt(1 - (N - n)/N)]\}m_0[1 - \exp[-kt(1 - (N - n)/N)]] \\ &= t_0m_0 \sum_{n=0}^N \{1 - \exp[-qt(n)/N]\}[1 - \exp[-kt(n)/N]] \\ &= t_0m_0 \sum_{n=0}^N \{1 - \exp[-qt(n)/N]\}[1 - \exp[-kt(n)/N]] \\ &= t_0m_0 \sum_{x_i=0}^1 \{1 - \exp[-qt x_i]\}[1 - \exp[-kt x_i]] \end{aligned} \tag{25.13}$$

where

$$x_i = n_i/N \tag{25.14}$$

and ranges from zero to unity.

To convert this to an integral, note Fig. 25.6 in which a graph of the sum is shown. As N goes towards infinity, the intervals become dx and the integral becomes

$$\begin{aligned}
 M_0 - M &= t_0 m_0 \int_0^1 \{1 - \exp[-qtx_i]\} [1 - \exp[-ktx_i]] dx \\
 &= M_0 - M = t_0 m_0 \int_0^1 \{1 + \exp[-(q+k)tx] \\
 &\quad - \exp[-qtx] - \exp[-ktx]\} dx \\
 &= t_0 m_0 \left[x - \{1/(q+k)t\} \exp[-(q+k)tx] + \{1/qt\} \exp[-qtx] \right. \\
 &\quad \left. + (1/kt) \exp[-ktx] \right]_0^1 \\
 &= t_0 m_0 \left\{ 1 + \{1/(q+k)\}t - \{1/(q+k)t\} \exp[-(q+k)t] \right. \\
 &\quad \left. - \{1/q\}t + \{1/q\}t \exp[-qtx] - (1/k)t + (1/k)t \exp[-ktx] \right\} \\
 &= t_0 m_0 t \left\{ J + (1/t) - \{1/(q+k)\} \exp[-(q+k)t] + \{1/q\} \exp[-qtx] \right. \\
 &\quad \left. + (1/k) \exp[-ktx] \right\}
 \end{aligned} \tag{25.15}$$

where

$$J = 1/(q+k) - (1/q) - (1/k) \tag{25.16}$$

Equation (25.15) is a rather complicated equation. If either disintegration or dissolution are rate-determining, then the equations become much more manageable. If, as is most often true, the disintegration is rapid, and then the process becomes

1. Rapid disintegration ($t = t_i$, the so-called lagtime)
2. Diffusion of drug from the granules

In such a case, the equation simply becomes:

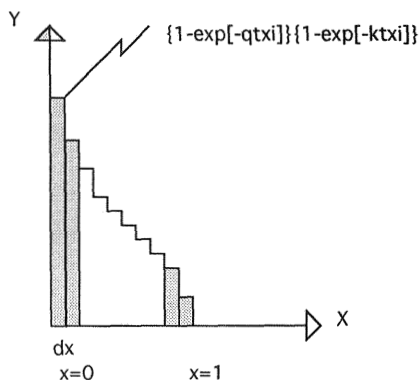


Fig. 25.6 Schematic of the trace of Eq. (25.13).

$$M_0 - M = 0 \quad 0 < t < t_i \quad (25.17)$$

$$\ln[M/M_0] = -k(t - t_i) \quad t > t_i \quad (25.18)$$

Most dissolution equations follow this path, and if the data are plotted according to Eqs. (25.17) and (25.18) then a straight-line ensues, which intersects $\ln[M/M_0] = 0$ at time $t = t_i$.

25.5. COMPRESSION-COATED AND MULTIPLE-LAYER TABLETS

Controlled-release of drugs from dosage forms will be discussed in detail in Chap. 26. However, one such principle, sustained-release by compression coating, is best discussed at this point in the text (Fig. 25.7) (Zoglio and Carstensen, 1985).

In this approach a tablet within a tablet within a tablet is created. Because each layer is not equally thick, the surface area, A , is approximately constant (and equal to the average between the surface area on the “outside” and “inside” of the layer. Hence, the rate equation (e.g., for the first layer) would be

$$dM/dt = -K(1)A(1) \quad (25.19)$$

where $K(1)$ is the dissolution rate constant and $A(1)$ is the average layer of the the outside (first) coat. This integrates to

$$M = M_1 - K(1)A(1)t \quad (25.20)$$

where M_1 is the original amount in the layer. Similarly, for the other two layers, using the same nomenclature

$$M = M_2 - K(2)A(2)t \quad (25.21)$$

and

$$M = M_3 - K(3)A(3)t \quad (25.22)$$

that is, an approximate linear release. This is now manipulated in such a fashion that $M_1 + M_2 + M_3$ is equal to the required dose, and the K values and the layer weights are manipulated in such a fashion that the amount released at various points in time (1, 4, and 8 h) are within the desired intervals.

Another approach is to make the outer coat a restraining coat, and this can be done, for instance, by using polymers, which are semipermeable both to the dissolving liquid, and to the drug substance, once it dissolves in the penetrated liquid (Conte et al., 1983; Verhoeven et al., 1989; Mars, 1974). The release of drug from

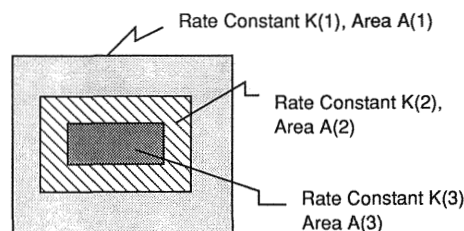


Fig. 25.7 Approximate linear release rates from tricoated tablet.

these is a function of such parameters as the amount of polymer, its surface characteristics, and its compressibility (Shivanand and Prockel, 1998). There are limitations to this (i.e., the effect of the compression pressure on the physical characteristics of the polymer), and Fryklof et al. (1967) employed soluble porosity modifiers to the (otherwise water-insoluble) compression coat so that, on exposure to dissolution liquid, these would dissolve and create a porosity network (Källstrand and Ekman 1983; Zenther et al., 1985; Thombre et al., 1989). However, the pore network, in some cases, and particularly with sorbitol, did not behave exactly as predicted. Stauffer (1985) applied percolation theory to the problem, and this was used (Siegel, 1988) to explain the development of pore clusters and conducting channels that would span the compression coat.

Shivanand and Sprockel (1998) have described a compression-coated tablet, for which the coating material was CAB and the porosity modifier was sodium chloride.

It would be expected that the release would be linear after a lag time and, indeed, this is what Shivanand and Sprockel (1998) found.

SYMBOLS

$A = A(1), A(2), A(3)$ = surface areas of the three parts of a tricoated tablet

g = gravitational acceleration

k = dissolution rate constant

k_d = disintegration rate constant

k_w = water uptake rate constant

k_s = disappearance rate constant of solid part of a tablet

$K = K(1), K(2), K(3)$ = the rate constants for each of the layers in a tricoated tablet

L = length of penetration (Washburn equation)

M = amount not dissolved or disintegrated

M_0 = original amount

m = exponent in Kitamori equation

N = tablets per second or number of disintegrated particles or number of time intervals

Q = constant (Washburn equation)

q, s = (a) fraction of time hopper stays over die; (b) or exponent in disintegration equation; (c) disintegration rate constant

r = pore radius

R = radius of disintegrant particle.

T = number of particles in a tablet

T_0 = initial number of particles in a tablet

t = time

t_g = disintegration time

W_s = weight (mass) of unhydrated tablet

W_w = mass of hydration part of a tablet

W_d = mass of tablet disintegrated

α = the angle between liquid and capillary wall

γ = interfacial tension

ϕ = contact angle

η = viscosity (of disintegration medium)

ρ = density

REFERENCES

- Berry H, Ridout CW (1950). *J Pharm Pharmacol* 2:619.
- Caramella C, Colombo P, Conte U, Gazzaniga A, LaManna A (1984). *Labo-Pharma Probl Technol* 339:115.
- Caramella C, Colombo P, Conte U, La Manna A (1987). *Drug Dev Ind Pharm* 13:2111.
- Carstensen JT (1976). Abstracts. *Am Pharm Assoc Acad Pharm Sci Natl Meeting* 21: (abst 6(2), paper 79).
- Carstensen JT (1995). *Drug Stability—Principles and Practices*. Marcel Dekker, New York, p 25.
- Carstensen JT, Wright JL, Blesel KW, Sheridan J (1978). *J Pharm Sci* 67:1303.
- Carstensen JT, Lai TY-F, Touré P, Sheridan J (1980). *Int J Pharm* 5:157.
- Carstensen JT, Kothari R, Chowhan ZT (1980a). *Drug Dev Ind Pharm* 6:569.
- Carstensen JT, Kothari R, Prasad VK, Sheridan J (1980b). *J Pharm Sci* 69:290.
- Cartilier L, Tawashi R (1993). *STP Pharma Sci* 3:213.
- Catellani PL, Predella P, Bellotti A, Colombo P (1989). *Int J Pharm* 51:63.
- Chebli C, Cartilier L (1998). *Int J Pharm* 171:101.
- Colombo P, Caramella C, Conte U, La Manna A, Guyot-Hermann AM, Ringard J (1981). *Drug Dev Pharm* 7:135.
- Colombo P, Conte U, Caramella C, Geddo M, La Manna A (1984). *J Pharm Sci* 73:701.
- Conte U, Colombo P, Caramella C, La Manna A (1983). *Press-Coated Systems for Drug Release Control*. Plenum, New York.
- Couveur P (1975). Dissertation, Docteur Sciences Pharmaceutiques. University Catholique de Louvain, Belgium, p 87.
- Faroongsamg D, Peck GE (1994). *Drug Dev Ind Pharm* 20:1777.
- Fryklof LE, Sandell E, Ostholm GIV (1967). Medicinal tablet and a method for its preparation. U. S. patent 3317394.
- Källstrand G, Ekman B (1983). *J Pharm Sci* 72:772.
- Kennon L, Swintosky JV (1958). *J Am Pharm Assoc Sci Ed* 47:397.
- Khan KA, Rhodes CT (1975). *J Pharm Sci* 65:1837.
- Kitamori N, Iga K (1978). *J Pharm Sci* 67:1436.
- Kitamori N, Shimamoto T (1976). *Chem Pharm Bull* 24:1789.
- Mars P (1974). Compositie met vertraagde afgifte. Dutch patent 7313696.
- Nogami H, Nagai T, Uchida H (1966). *Chem Pharm Bull* 14:152.
- Poukavos N, Peck GE (1993). *Pharm Res* 10:13363.
- Sheen P, Kim S (1989). *Drug Dev Ind Pharm* 15:401.
- Shivanand P, Sprockel OL (1988). *Int J Pharm* 167:83.
- Siegel RA (1988). In: Rosoff M, ed. *Controlled Release of Drugs*. VCH, New York.
- Stauffer D (1985). *Introduction to Percolation Theory*. Taylor & Francis, Philadelphia.
- Thombre AG, Zentner GM, Himmelstein KJ (1989). *J Membr Sci* 40:279.
- Timmermans J, Lievin V, Moes AJ (1995). *STP Pharma Sci* 5:110.
- Van Kamp HV, Bolhuis GK, De Boer AH, Lerk CF, Lie-a-huen L (1986). *Pharm Acta Helv* 61:221986.
- Verhoeven J, Schutte SC, Peschier LJC, Danhof M, Junginger HE (1989). *J Controlled Release* 10:205.
- Wan LSC, Choong YL (1986). *Pharm Acta Helv* 61:150.
- Zentner GM, Rork GS, Himmelstein KJ (1985). *J Controlled Release* 2:217.
- Zoglio MA, Carstensen JT (1985). *Int J Pharm Technol Prod Manuf* 5:1.

RECOMMENDED READING

Rudnic EM, Kottke MK (1989). In: Banker GS, Rhodes CT, eds. *Modern Pharmaceutics*. Marcel Dekker, New York, pp 348–354.

Lieberman HA, Lachman L, Schwartz JB (1989). *Pharmaceutical Dosage Forms: Tablets*, 2nd ed. Marcel Dekker, New York, vols 1, 2, and 3.

26

Polymers

26.1.	Molecular Weights of Polymers	440
26.2.	Intrinsic Viscosity	440
26.3.	Polyethylene Glycols	441
26.4.	Cellulose and Cellulose Derivatives	441
26.5.	Intrinsic Viscosity and Molecular Weight	442
26.6.	Polymethacrylates	444
26.7.	Polyvinylpyrrolidone	444
26.8.	“Older” Polymers	444
26.9.	Methylcellulose (MC) and Hydroxypropyl Methylcellulose (HPMC)	444
26.10.	Hydroxypropyl Cellulose (HPC)	445
26.11.	Ethyl Cellulose (EC)	446
26.12.	Diffusion Through Films	446
26.13.	Plasticizers	448
26.14.	Cellulose Acetate Derivatives	449
26.15.	Other Polymers	449
26.16.	pH and Temperature-Sensitive Polymers	450
	Symbols	451
	References	451

Polymers constitute a special group of excipients, and their prime uses are the following:

1. Granulating agents

2. Film-coating materials
3. Release-sustaining excipients

The latter will be the subject of Chap. 29, whereas in this chapter, the properties of the polymers of interest will be discussed.

26.1. MOLECULAR WEIGHTS OF POLYMERS

The important polymers in sustained release are (a) ethyl cellulose (Ethocel; EC), (b) hydroxypropyl methylcellulose (Methocel; HPMC), and (c) hydroxypropylcellulose (Klucel (HPC)).

The manner in which the molecular weight is determined is by preparing dilute solutions of it in an appropriate solvent (for HPMC and HPC, water) and measuring the osmotic pressure.

The ideal gas law states that

$$PV = nRT \quad (26.1)$$

where V is volume, P is pressure, n is number of moles, R is the gas constant, and T is absolute temperature ($^{\circ}\text{K}$). The ideal gas law also applies to very dilute solutions, in which the concentration C of solute, is n/V , so that Eq. (26.1) becomes

$$\Pi = RTC \quad (26.2)$$

where Π is the osmotic pressure. If the concentration is expressed as C^* in grams per mole of solvent, then, at low concentrations, the osmotic pressure will become linear with concentration, C^* . If C had been in moles per mole of solvent, then the slope should have been RT , and the ratio between the slope found (by using C^*) and RT will then allow calculation of the molecular weight.

Because determination of molecular weight becomes a specification in lots of polymer, easier means of obtaining it are important.

26.2. INTRINSIC VISCOSITY

The definition of *viscosity*, in its most basic form, is visualized by an infinitely wide vessel containing the test liquid and providing a moving plate above a stationary bottom (Fig. 26.1). To move the plate at a given speed v , requires a given force F , and this force is inversely proportional to the distance of the movable plate from the

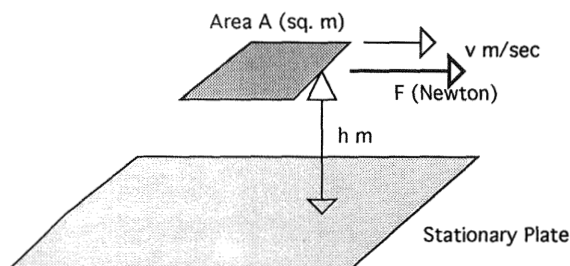


Fig. 26.1 Schematic for the definition of viscosity.

stationary bottom. It is also directly proportional to the surface area of the movable plate ($A \text{ cm}^2$).

The force required to move the plate is equal to the viscosity of the liquid, if $A = 1$ and $h = 1$, the definition of intrinsic viscosity is

$$[\eta] = \lim_{C \rightarrow 0} \{[(\eta/\eta^0) - 1]/C\} \quad (26.2)$$

where η^0 is the viscosity of the pure solvent.

Viscosity in the cgs-system is measured in poise (P), and the most common unit is the centipoise (cp). The viscosity of water at room temperature is about 1 cp.

Often the *kinematic* viscosity is employed. This is the viscosity divided by the density of the liquid; that is,

$$\eta = \eta/\rho \quad (26.3)$$

The unit for this is *stoke* or *centistoke*.

Viscosity is often measured by monitoring the shear rate as a function of the shear stress, and if such a plot is linear, then the liquid is denoted *newtonian*. If not, then it may be either *thixotropic*, *dilatant*, *pseudoplastic*, or a *Bingham body*. In the first two cases, the viscosity changes when the liquid is shaken (or otherwise subjected to stress). For the pseudoplastic liquids, the shear rate is a power function of the shear stress, and for the Bingham body, there is a *yield value*, below which the liquid does not move under stress. Polymers in concentrations of less than 1% v/v are usually newtonian.

Molecular weights of polymers may also be obtained by gel permeation chromatography.

26.3. POLYETHYLENE GLYCOLS

The notation for polyoxyethylene glycols is PEG, and they are usually referred to as polyethylene glycols. They vary in consistency from liquids to solids. The notation PEG is followed by a number indicating an approximation of the molecular weight. The molecular weights range from 190 to 20,000. The most common grades are shown in Table 26.1.

26.4. CELLULOSE AND CELLULOSE DERIVATIVES

Many of the useful polymers are either cellulose itself (microcrystalline cellulose [MCC], which is covered under direct compression) and derivatives of cellulose

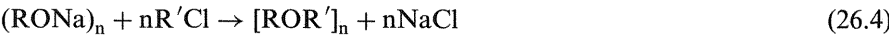
Table 26.1 Characteristics of Polyethylene Glycols

Notation	Molecular weight	State at 25°C
PEG 400	380–420	Liquid
PEG 1000	950–1050	Solid
PEG 4000	300–4800	Solid
PEG 6000	5400–6600	Solid

are used as film-coating materials, as binding agents, and as excipients imparting sustained action to dosage forms. Powdered cellulose is marketed as Solkafloc or Elcema. The derivatives' primary use is as tablet (or capsule) excipients. A micro-crystalline grade (MCC) is used as a direct compression excipient.

26.5. INTRINSIC VISCOSITY AND MOLECULAR WEIGHT

Cellulosic polymers are $[\text{ROR}']_n$, where n is the degree of polymerization, R is the cellulosic saccharide unit, and R' the substituent; e.g., hydrogen or methyl). They are often obtained by placing cellulose $[\text{ROH}]_n$ in alkali to form $[\text{RONa}]_n$ and then reacting it with the appropriate chloride, $R'\text{Cl}$ (e.g., methyl chloride):



Placing the cellulose in alkaline solution causes some deterioration of the cellulose, so that there will be a host of cellulose sodium salts with different chain lengths. Hence, the n , in $[\text{ROR}']_n$ is not a single figure, but constitutes several values. If the molecular weight of one of the molecular segments of $[\text{ROR}']$ is M_i , then the number molecular average weight M_n , is given by

$M_n = \Sigma f_i n_i M_i / \Sigma f_i n_i$ (26.5)

where f_i is the number fraction of molecules having a degree of polymerization of n_i . By the same token, the *weight molecular average weight* is given by using the weight fraction, f_i^w , of molecules with a degree of polymerization of n_i .

$M_w = \Sigma f_i^w n_i M_i / \Sigma f_i^w n_i$ (26.6)

The value of M_n is often obtained by way of the so-called Mark–Houwink equation, which states that

$[\eta] = KM_n^\sigma$ (26.7)

where K is a function of the polymer and σ is an exponent that is a function of the shape of the molecule. Rowe (1982) has listed the values of K and σ for a series of polymers. Table 26.2 is reconstructed from the cited publication.

A less exacting, but often used, manner of correlation is rather than use the intrinsic viscosity, to use the viscosity of a given concentration of polymer, for instance (as in the Dow Chemical Company's bulletins on HPMC), using a 2%

Table 26.2 Mark–Houwink Constants for Derivatives of Cellulose, Used in Sustained-Release Formulations and in Film Coating

Polymer	Solvent	10^{-3} dL g ⁻¹	σ	$10^{-4} \times \text{MW range}$	Ref
MC	Water	316	0.55	12–57	Neely, 1963
HPC	Ethanol	2.6	0.92	18–126	Wirick, 1970
HPMC	Water	99.4	1.10	3–20	Rowe, 1980; Moore, 1955
EC	CCl ₄	11.8	0.89	4–14	Brown, 1958
	C ₆ H ₆	29.2	0.81	4–14	Greminger and Savage, 1959

Source: Rowe, 1982.

aqueous solution and correlating this with the molecular weight. Often such graphs are presented in the form

$$\ln[M_n] = \beta \ln[\eta] \tag{26.8}$$

that is,

$$\beta = 1/\sigma \tag{26.9}$$

Table 26.3 lists the viscosity of grades of HPMC as a function of the number average molecular weight of the polymer M_n , and these two quantities relate to one another by Eq. 26.8:

When the table figures (the last two columns) are plotted in this fashion, Fig. 26.2 results.

The least-squares fit line is $y = 1.8363 + 0.31382x$; $R^2 = 0.999$. For instance, if an HPMC had a (2% aqueous) viscosity of 100,000, then, if the value $\ln[100,000] = 11.5$ could be inserted in the equation, and the value of $\ln[M_n]$ found to be $y = 5.44523$, or $M_n = 232$ (i.e., an M_n value of 232,000) could be estimated.

Frequently the nominal viscosity (η^*) is used and is defined as:

$$\eta^* = (\eta/\eta^0) - 1 \tag{26.10}$$

In this case (Rowe 1982), the Mark–Houwink equation takes the form

$$MW = K^*[\eta^*]^q \tag{26.11}$$

Rowe states that

This equation is very useful to the formulator since it can be used to predict molecular weight of samples of known nominal viscosity. It is interesting to note that the molecular weight for the N100 sample (nominal viscosity 88 mPaS—Table 2) predicted using this equation was 8.12×10^4 compared with 7.1×10^4 measured by gel permeation chromatography.

Table 26.3 Viscosity of 2% Solutions

Viscosity 2% solution	Number Avg Mol Wt, $M_n \times 10^{-3}$	$\ln[\eta]$	$\ln[MW/1000]$
10	13	2.303	2.565
40	20	3.689	2.996
100	26	4.605	3.258
400	41	5.991	3.714
1,500	63	7.313	4.143
4,000	86	8.294	4.454
8,000	110	8.987	4.700
15,000	120	9.616	4.787
19,000	140	9.852	4.942

Molecular weight calculated from osmotic pressure as concentration approaches zero.
Source: *Encyclopedia of Polymer Science and Technology*, 3, p 504, Interscience, John Wiley & Sons, New York, 1965, p 504). The designation method is described in ASTM monographs D1347-72 and D2363-72. Data from Dow Manuals.

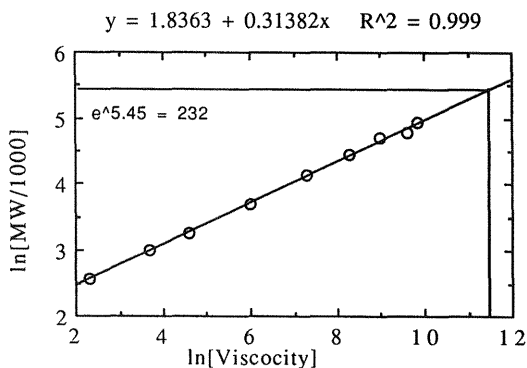
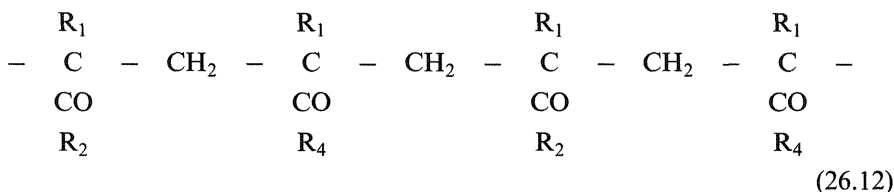


Fig. 26.2 Data in Table 26.3 plotted according to Eq. (26.8).

26.6. POLYMETHACRYLATES

Polymethacrylates are substituted polymers of acrylic acid (anhydride) and have the general formula:



where the substituents determine the properties of the polymer. They are known, commercially, as *Eudragits*.

26.7. POLYVINYLPIRROLIDONE

Polyvinylpyrrolidone, also known as *povidone* or PVP is used as a tablet binder and as a rigid matrix in sustained-release preparations.

26.8. "OLDER" POLYMERS

The original sustained-release product patented by Smith Kline & French in 1950, used shellac as a sustaining agent. Owing to its tendency to polymerize on storage, it is, by now, largely abandoned in new formulations. Other compounds (e.g., hydrogenated castor oil) have been used, but a different set of polymers are nowadays most often considered in new product formulation, and these will be dealt with, in the following

26.9. METHYLCELLULOSE (MC) AND HYDROXYPROPYL METHYLCELLULOSE (HPMC)

The abbreviated names in parentheses in the heading will be used often in the following, as they have been in the text preceding this. It was mentioned in an earlier chapter that HPMC may be used as a granulating agent (e.g., as a particle size

enlarger and as a binder), but the most interesting use of the polymers is in creating sustained-release dosage forms.

HPMC and HPC are marketed by Dow Chemical Company, and there are various grades as shown in Table 26.4. The data in this table are reconstructed from data in Methocel Bulletin, *Formulating Sustained Release Pharmaceutical Products with METHOCCEL*, 1982. As mentioned, they are characterized by the viscosity of a 2% aqueous solution, as shown in Table 26.4.

There are manufacturers other than Dow Chemical Company (e.g., British Celanese, Ltd, England). Metolose SH is the tradename used by Shin-Etsu, Ltd, Japan. The viscosities are from 15 to 100,000 cp, and these viscosities correspond to number average molecular weights from 10,000 to 190,000. A given trade name is an HPMC with a single viscosity (e.g., 100 cp, 4000 cp, and so on) as shown in Table 26.4. Recent grades have molecular weights as high as 240,000.

Attempts have been made to *modify HPMC* to tailor-make it to certain sustained-release requirements. Schor, in a series of patents (Schor, 1978, 1979, 1981, 1982), hydrolyzed HPMC (Methocel E-50) by exposing it to high humidity. U. S. patent 3,870,790 employs up to 25% moisture and then obtains sustained release by controlling the degree of compression. In the invention as little as 0.5% could be present. Although the actual mechanism is unknown, Schor (1981) speculated that the slower-release rate arises from a decreased rate of swelling or a lower water solubility resulting from hydrogen-bonding interaction between the carboxyl and the carbonyl groups that had been subjected to both hydrolysis and oxidation. He further improved the carrier base utilizing a grade HPMC with the following characteristics: Methocel K4M and K15M; and in one case K100, MW > 50,000, with a methoxyl content of 16–24 wt%. The molecular weights were higher at the time than those used in the past and he used an amount of modified HPMC less than about one-third of the weight of the sustained-release dosage form. In all cases the carrier material was thoroughly intermixed with the medicament which was either powder or in solution.

26.10. HYDROXYPROPYL CELLULOSE (HPC)

This is often used in combination with Ethocel, and sometimes acts as a plasticizer for the Ethocel.

Table 26.4 Various Grades of Methyl and Hydroxymethyl Propylcellulose

Methylcellulose (Methocel), USP (A-series)	
Methocel A4M Premium	4,000 cp
XD-30345.01	18,000 cp
HPMC, USP 2208 (K-series)	
Methocel K4M Premium	4,000 cp
Methocel K15M Premium	15,000 cp
XD-30018.00 (K-100M Premium)	100,000 cp
HPMC, USP 2910 (E-series)	
Methocel E4M Premium	4,000 cp
HPMC, USP 2905 (F-series)	
Methocel, F4M Premium	4,000 cp

Samuelov et al. (1979) have described a laminated, double-layer film with a drug-containing layer that incorporates the drug in HPC attached to a film containing EC with different percentages of either polyethylene glycol (PG) or HPC. Zero-order release of the drug substances (tripelenamine, barbital, salicylic acid, or caffeine) was reported.

26.11. ETHYL CELLULOSE (EC)

Ethyl cellulose (EC) is cellulose that is ethylated (i.e., forms ethyl ether bonds) at the OH groups in cellulose. There are various degrees of ethylation, giving products with different viscosities. This latter is determined in a solvent consisting of a 4 : 1 ratio, by weight, of toluene/ethanol, using ethyl cellulose samples dried for 30 min at 100°C. Table 26.5 shows the ethoxyl (E) contents and the amount of ethoxyl/glucoses unit (E/A) of various grades from Hercules Company.

The extent moisture adsorption of ethyl cellulose goes down as the ethoxyl content goes up in the range of 43–51%. In this range, the hardness and the softening point show a minimum when the ethoxyl content is 48%. Ethyl cellulose is soluble in ethanol when the ethoxyl content is 45–49%, but requires a 4 : 1 toluene/ethanol as a solvent when the ethoxyl content is 48–51%.

If different types are compared, and the yardstick is the viscosity of a 5% solution in 4 : 1 toluene/ethanol then the following properties increase with increasing viscosity: tensile strength, percentage elongation at rupture, and flexibility.

As a film former, it is important to keep water out of the solvent system, because it accumulates in the solution on evaporation and forms a spongy, porous film (Arwidsson and Johansson, 1991).

Ethocel is particularly useful in microencapsulation. Alam and Eichel (1982) have described sustained-release pharmaceutical formulations of indoprofen in microparticles coated with ethyl cellulose.

HPC and HPMC are often used in blends with EC in the formulation of microencapsulation-based sustained- or delayed-action systems (Rowe, 1980), as is PEG.

26.12. DIFFUSION THROUGH FILMS

In sustained-release products, the diffusion of water and oxygen through polymers is of importance.

Consider a microcapsule in which liquid has permeated into the interior and has become saturated with drug substance. In that situation, the concentration of

Table 26.5 Ethoxy Content of Various Ethocel Grades

Grade	G	K	N	Y
Ethoxyl (E)	44.5–45.5%	45.5–46.8%	47.5–4.90%	> 49%
E/Anydroglucose unit	2.21–2.28	2.28–2.38	2.42–2.53	> 2.53

Source: Hercules Co., 1966.

drug in the liquid (on the “left”) in Fig. 26.3 will be its solubility S_1 in the liquid. The concentration at the exit side of the film, at sink conditions, will be zero, so that Fick’s first law will require that

$$dM/dt = DAS_2/h \quad (26.13)$$

where S_2 is the concentration of drug in the film on the donor side; D is the diffusion coefficient; A is the surface area of the film; M is the amount released at time t ; and h is the film thickness. Eq. (26.13) integrates to

$$M = (DAS_2/h)t \quad (26.14)$$

The value of the concentration S_2 of the drug in the polymer on the entry side is given by the partition law as

$$S_2 = QS_1 \quad (26.15)$$

where Q is a partition coefficient. This inserted in Eq. (26.14) gives

$$M = (DAQS_1/h)t = (\Pi S_1/h)t \quad (26.16)$$

where Π is the permeability and is given by

$$\Pi = QD \quad (26.17)$$

A plot of M versus t should therefore, *under sink conditions on the exit side and saturation on the entry side of the membrane*, be linear, and the slope β , should be

$$\beta = (\Pi S_1/h) \quad (26.18)$$

When there is no saturation (i.e., when no solid drug phase is left on the entry side), then S_1 is not only smaller than saturation, but will also change with time.

From the foregoing equations it is possible to calculate the value of the permeability constant from plots according to Eq. (26.16). Figure 26.4 is constructed from data published by Donbrow and Friedman (1974).

Donbrow and Friedman (1974) established that mass transfer through ethyl cellulose is controlled by a solubility diffusion process, such as described in the

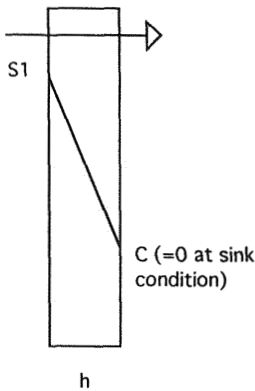


Fig. 26.3 Schematic of diffusion of a drug through a film. The solution is saturated on the entry side (to the “left”), and the concentration in the liquid on the exit side (to the “right”) is assumed to be zero when sink conditions prevail.

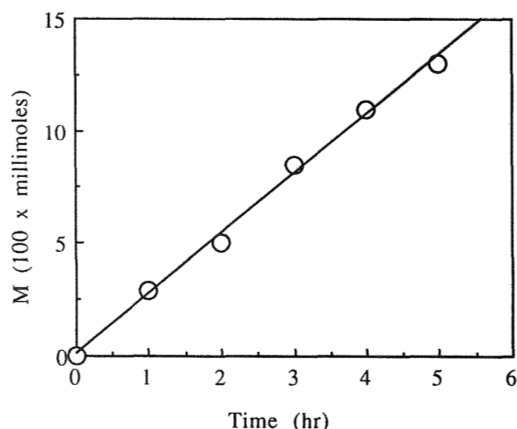


Fig. 26.4 Transfer of caffeine through an ethyl cellulose film containing 50% PEG. (Data from Donbrow and Friedman, 1974.)

foregoing, when PEG 4000 is used as an additive to the film. With inclusion of PEG 4000 (which acts as a plasticizer) there is an increase in permeability, apparently because the PEG dissolves in the aqueous intrusion phase and, thereby, increases porosity. This is equivalent to a reduction in the thickness of the film.

The leaching of PEG 4000 was confirmed by Samuelov and co-workers (1979), who found, however, that the release profile of tripeleennamine HCl through PEG-ethyl cellulose films followed a Higuchi law (Higuchi, 1961). These authors mentioned that, in contrast to PEG, HPC when used as an additive, was not leachable.

26.13. PLASTICIZERS

Most of the mentioned polymers are amorphous to a large or small degree. Plasticizers are usually used in applications to make the film more pliable and less likely to break. A plasticizer works by lowering the glass transition temperature T_g of the polymer, so that it lowers the temperature at which the plasticizer will be in a rubbery phase. The rubbery phase, as the name implies, is less brittle than the glass phase.

Glass transition temperatures are usually determined by differential scanning calorimetry (DSC). Sakellariou et al. (1986) used a torsional braid balance to study the glass transition temperatures of mixtures. This method is, when used for films, much more sensitive than DSC. If the glass transition is lowered by the addition of a compound, this latter acts as a plasticizer. If not, then there is mutual insolubility between film former and additive, and this is important in EC films. In contact with water, a soluble additive will form channels in the film, and dissolve in contact with the water of intrusion. The film is left with "holes" which will allow diffusion of drug from the interior of a microcapsule. If the additive is insoluble, then such holes will not occur, although the film may erode more readily.

The use of Ethocel, containing either HPC or PEG as a coating material for potassium chloride has been quite successful. Microcapsules prepared either by solvent method or by spray-coating can be made with films of very high tensile strength

(Chang and Rudnic, 1991). Hsiao and Chou (1989) had earlier described a similar process for controlled release of potassium chloride. By using Ethocels of high molecular weight, *microcapsules could be produced that lend themselves to tableting without rupturing the film*. This is of great importance, because before that time, tableting was considered impossible because cracks in the film would destroy the controlled, sustained effect of the individual microcapsules.

Holliday et al. (1970) have described microcapsules of aspirin using ethyl cellulose, and found that although the in vitro release was prolonged to 4 h, the in vivo release from pain was prolonged by 8 h.

Deasy et al. (1980), microencapsulated sodium salicylate with ethyl cellulose 100 cp, by polymer deposition from cyclohexane by temperature change, and obtained a product that was finer and had a longer sustained action than when a 10 cp grade of EC was used.

26.14. CELLULOSE ACETATE DERIVATIVES

Cellulose acetate phthalate was, for many years, the best enteric-coating compound. It is insoluble in acid, but soluble at pH values in excess of 4.5–5. In this manner a coat may be placed about a tablet, which will then not dissolve in the stomach, but will dissolve in the intestinal tract. The principle is also applicable to beads.

Shivanand et al. (1998) have described compression-coated tablets, for which the coating material was *cellulose acetate butyrate*. Controlling the release was accomplished by adding water-soluble compounds, whereby the outer layer would become porous; the most often used porosity modifier was sodium chloride.

26.15. OTHER POLYMERS

Alginic acid—sodium alginate, sodium polymannuronate—is used as a disintegrating agent and tablet binder.

Sodium starch glycolate is used as a tablet and capsule disintegrant. It is sold, commercially, as Explotab and Primojel. It is the sodium salt of the carboxymethyl ether of starch.

Cellulose acetate phthalate is used as an enteric coat. The $-\text{CH}_2\text{OH}$ and OH groups in cellulose are substituted with either acetyl or phthalyl, one OH and one $-\text{CH}_2\text{OH}$ in four glucose units being left unsubstituted.

Carboxymethylcellulose sodium (CMC) is used as a thickener in liquid formulation, but also serves as a (mild) disintegrant in tablet formulations.

Carbopol (carboxypolyethylene) is a carboxyvinyl polymer that has been used in various products in the past (e.g., the appetite depressant *Tenuate Dospan*, marketed in years past by Merrell Labs).

Gelatin, a natural product derived from animal hide or bone, is a mixture of fractions of amino acid groups that are tied together through peptide linkages. The polymers are linear and have molecular weights from 15,000 to 250,000. Gelatin is produced by hydrolysis, which can be either acid or alkaline. The isoelectric point is a function of the treatment.

There are numerous *polysaccharides* of pharmaceutical interest. Notably of these is *guar gum*, which is a galactomannan polysaccharide, with molecular weight about 220,000.

Poly(DL-lactic acid) is used as a matrix-sustaining ingredient employing wet granulation techniques in amounts of as low as 5–15% w/w poly(DL-lactic acid). Properties such as glass transition temperature and molecular weights have been reported (Omeltczuk and McGinity, 1992; Coffin et al., 1987). Steendam and Lerk (1998) have used it as a direct-compression excipient in controlled-release tablets, with good results.

The drug release mechanism from poly(D,L-lactide) or poly(D,L-lactide-co-glycolide) has been described (Hutchinson and Fur, 1990; Jalil and Nixon, 1990; Yamakawa et al., 1990; Fitzgerald and Corrigan, 1996; Hsu et al., 1996a,b). As in other cases, the release of drug from systems of this kind is a function of both drug diffusion and matrix erosion (Sanders et al., 1986; Sato et al., 1988; Asano et al., 1989; Fitzgerald and Corrigan 1996; Hsu et al., 1996 a,b).

Sung et al. (1998) have described aliphatic polyesters on a base of lactide–glycolide copolymers. A series of compounds have been incorporated into this type of matrix (Ike et al., 1992; Mauduit et al., 1993; Niwa et al., 1993; Zhang et al., 1993; Aso et al., 1994; Lambert and Peck, 1995; Chandrashekar and Upada, 1996).

Vervoot (1998a,b) has described the use of *inulin hydrogels*. Inulin is a naturally occurring polysaccharide found in many plants (Van Loo et al., 1995); chemically, it is linked fructose molecules, a certain number of which have a glucose molecule at one chain end (Roberfroid, 1993).

Fernández-Hervás et al. (1998) have described an *alginate–Eudragit L30D* system for sustained release. The beads are prepared in the following manner: 1.5 aqueous alginate solution is prepared, and a solution of the drug added. The Eudragit is dissolved separately by use of a small amount of sodium hydroxide (neutralizing it to an extent of 30%). This partially dissolves the polymer and is added to the alginate solution. Calcium chloride (1.3% w/w) is then added. The reaction product is stored at 22°C for 24 h until the reaction has completed. The microspheres that are formed are then filtered off and dried.

Talukar et al. (1998) have described *xanthan gum* as a potential use in oral sustained-release matrices. They demonstrated its use in indomethacin formulations.

There are some advantages to including both hydrophilic and hydrophobic moieties into backbone polymers (Serres et al., 1996); for instance, some polymers, such as *poly(N-isopropylacrylamide)*, and similar N-substituted acrylamides, possess a lower critical solution temperature. Therefore, they swell reversibly at low temperatures and swell only slightly at higher temperatures (Hoffman et al., 1986; Bae et al., 1990; Dong et al., 1990).

Pluronic F-127 is a polyoxyethylene–polyoxypropylene copolymer, and it forms an aqueous hydrogel above 32°C (Lenaerts et al., 1987; Miyazaki et al., 1987).

26.16. pH AND TEMPERATURE-SENSITIVE POLYMERS

The oldest of these are *shellac* and *cellulose acetate phthalate* (CAP). In some cases the swelling of a polymer is pH-dependent (Siegel et al., 1988; Brannon-Peppas and Peppas, 1989; Kim et al., 1994). With engineered cross-linking it is possible to make pH/temperature-sensitive hydrogels. These so-called *heterogels* combine, through cross-linking, the qualities of pH- and temperature-dependent hydrogel properties (Dong et al., 1990, 1992, 1994).

Polyvinylacetal diethylaminoacetate has been described by Aikawa et al. (1998). It is pH-sensitive and has been used for microencapsulation and for film coating (Shinkuma et al., 1991; Shimano et al., 1993). It is insoluble in water, but is soluble in gastric juice.

Polyvinyl alcohol is used primarily as a suspending or viscosity-enhancing ingredient in liquid formulations.

SYMBOLS

A = diffusional area

C = molality (moles solute per mole solvent)

D = diffusion coefficient

EC = ethyl cellulose

f_i = number fraction of cellulosic derivative molecules with molecular weight M_i

f_i^w = weight fraction of cellulosic derivative molecules with molecular weight M_i

HPC = hydroxypropylcellulose

HPMC = hydroxypropyl methylcellulose

h = film thickness

MC = Methocel, methylcellulose (often a type of HPMC)

M = (a) molecular weight of cellulosic unit; (b) mass diffused

M_n = number average molecular weight

M_w = weight average molecular weight

n = number of moles

P = pressure

R = the ideal gas constant

$[\text{ROH}]_n$ = cellulose

ROR'_n = substituted cellulose where n is the degree of polymerization

$[\text{ROR}']$ = substituted cellulose unit

R' = substituent in substituted cellulose

S_2 = drug concentration in the polymer directly inside the entry side

S_1 = drug concentration directly on outside of entry side of polymer

T = absolute temperature (K)

t = time

V = volume

β = (a) $1/\sigma$, exponent in intrinsic viscosity versus molecular weight; (b) slope of diffusion plot ($= (A\Pi S_1/h)$)

η = viscosity of solution of polymer

η^0 = viscosity of pure solvent

$[\eta]$ = intrinsic viscosity

Π = (a) osmotic pressure; (b) permeability

REFERENCES

- Alam AS, Eichel HJ (1982). U. S. patent 4,316,884.
 Aikawa K, Matsumoto K, Uda H, Tanaka S, Shimamura H, Arwidsson H, Johansson B (1991). *Int J Pharm* 76:91.

- Asano M, Fukuzaki M, Yoshida M, Kumakura M, Mashimo T, Yuasa H, Imai K, Yamanaka H, Suzuki K (1989). *J Controlled Release* 9:111.
- Aso Y, Yoshioka S, Po ALW, Terao T (1994). *J Controlled Release* 31:33.
- Bae YH, Okano T, Kim WW (1990). *J Polym Sci B Polym Phys* 28:923.
- Brannon-Peppas L, Peppas NA (1989). *J Controlled Release* 8:267.
- Chandrashekar G, Udupa N (1996). *J Pharm Pharmacol* 48:669.
- Chang R-K, Rudnic EM (1991). *Int J Pharm* 70:261.
- Coffin MD, Bodmeier R, Chang KT, McGinity JW (1987). *J Pharm Sci* 76:261.
- Deasy PB, Brophy MR, Ecanow B, Joy MM (1980). *J Pharm Pharmacol* 32:15.
- Donbrow M, Friedman M (1974). *J Pharm Pharmacol* 27:633.
- Dong LC, Hoffman AS (1990). *J Controlled Release* 13:21.
- Dong LC, Yan Q, Hoffman AS (1992). *J Controlled Release* 19:171.
- Dong LC, Hoffman AS, Yan Q (1994). *J Biomater Sci Polym Ed* 5:473.
- Dow Handbook on Methocel Cellulose Ether Products. [Table headed "Viscosities of Methylcellulose of Various Molecular Weights].
- Dow Information Sheet (1982). METHOCEL. No. 192-886-682. British Patent, 1070492.
- Fernández-Hervás MJ, Vela MT, del Cerro J (1995). *Int J Pharm* 113:39.
- Fernández-Hervás MJ, Holgado MA, Fint A, Fell JT (1998). *Int J Pharm* 163:23.
- Fitzgerald JF, Corrigan OI (1996). *J Controlled Release* 42:125.
- Greminger GC, Savage AB (1959). In: Whistler RL, ed. *Industrial Gums—Polysaccharides and Their Derivatives*. Academic Press, New York, pp 565–596.
- Hoffman AS, Afrassibi AA, Dong LC (1986). *J Controlled Release* 4:213.
- Holiday WM, Berdick M, Bell SA, Kirit GC (1970). U. S. patent 3,488,418.
- Hsiao C, Chou T (1989). U. S. patent 4,863,743.
- Hsu YY, Gresser JD, Trantolo DJ, Lyons CM, Gangadharam PRJ, Wise DL (1996a). *J Controlled Release* 40:293.
- Hsu YY, Gresser JD, Stewart RR, Trantolo DJ, Lyons CM, Simons GA, Gangadharam PRJ, Wise DL (1996b). *J Pharm Sci* 85:706.
- Hutchinson FG, Furr ABJ (1990). *J Controlled Release* 13:279.
- Ike O, Shimizu Y, Wada R, Hyon SH, Ikada Y (1992). *Biomaterials* 13:230.
- Jalil R, Nixon JR (1990). *J Microencapsul* 7:53.
- Kim YH, Bae YH, Kim SW (1994). *J Controlled Release* 28:143.
- Lambert WJ, Peck KD (1995). *J Controlled Release* 33:189.
- Lenaerts V, Triqueneaux C, Quarton M, Rieg-Falson F, Couvreur P (1987). *Int J Pharm* 39:121.
- Mauduit J, Bukh N, Vert M (1993). *J Controlled Release* 25:43.
- Miyazaki S, Nakamura T, Yokouchi C, Takada M (1987). *Chem Pharm Bull* 35:1243.
- Moore WR, Brown AM (1958). *J Appl Chem* 8:363.
- Neeley WB (1963). *J Polym Sci A1*:311.
- Niwa T, Takeuchi H, Hino T, Kunou N, Kawshima Y (1993). *J Controlled Release* 25:89.
- Omelczuk MO, McGinity JW (1992). *Pharm Res* 9:26.
- Roberfroid MB (1993). *Crit Rev Food Sci Nutri* 33:103.
- Rowe RC (1980). *J Pharm Pharmacol* 32:116.
- Rowe RC (1982). *Int J Pharm Technol Prod Manuf* 3:111.
- Rudin A, Wagner RA (1975). *J Appl Polym Sci* 19:3361.
- Sakellariou P, Rowe RC, White EFT (1985). *Int J Pharm* 27:267.
- Samuelov Y, Donbrow M, Friedman M (1979). *J Pharm Sci* 68:325.
- Schor JM (1979). U. S. patent 4,226,849.
- Schor JM (1981). U. S. patent 4,357,469.
- Schor JM (1982). U. S. patent 4,389,393.
- Schor JM, Nigalaye A, Gaylord NG (1981). U. S. patent 4,369,172.
- Serres A, Baudys M, Kim SW (1996). *Pharm Res* 13:196.

- Shimano K, Kaondo O, Miwa A, Higashi Y, Koyama L, Yoshida T, Ito Y, Hirose J, Goto S (1993). *Yakuzaigaku* 53:271.
- Shinkuma D, Hamaguchi T, Kobayashi T, Yamanaka Y, Mizuno N (1991). *Int J Clin Pharmacol Ther Toxicol* 29:303.
- Siegel RA, Firestone BA (1988). *Proc Symp Controlled Release Bioact Matter* 15:164.
- Steendam R, Lerk CF (1998). *Int J Pharm* 175:33.
- Sung KC, Nixon PR, Skoug JW, Ju TR, Gao P, Topp EM, Patel MW (1998). *Int J Pharm* 142:53.
- Talukar MM, Van den Mooter G, Augustijns P, Tjandra-Maga T, Verbeke N, Kinget R (1998). *Int J Pharm* 169:105.
- Van Loo J, Coussement P, De Leenheer L, Hoebregs H, Mits G (1995). *Crit Rev Food Sci Nutr* 36:525.
- Vervoort L, Van den Mooter G, Augustijns P, Kinget R (1998a). *Int J Pharm* 172:127.
- Vervoort L, Rombaut P, Van den Mooter G, Augustijns P, Kinget R (1998b). *Int J Pharm* 172:137.
- Wirick MB, Waldman MH (1970). *J Appl Polym Sci* 14:579.
- Yamakawa I, Kawahara M, Watanabe S, Miyake Y (1990). *J Pharm Sci* 79:505.
- Zhang X, Wyss UP, Pichora D, Amsden B, Goosen MFA (1993). *J Controlled Release* 25:61.

This Page Intentionally Left Blank

27

Coating of Tablets

27.1. Sugar Coating	456
27.2. Origin of Film Coating: Organic Solvent Coating	456
27.3. Enteric Coatings	457
27.3.1. Defects	457
27.4. Plasticizers	459
27.5. Glass Transition Temperatures	460
27.6. Strength of Films and Effect of Storage	460
27.7. Solvent System	462
27.8. Aqueous Film Coating	463
27.9. Properties of Aqueous Films	464
27.10. Sustained-Release Coatings on Tablets	465
Symbols	467
References	467
Recommended Reading	468

Coating tablets has several purposes.

1. It is a barrier to moisture and (possibly) oxygen, rendering the encased drug substance more stable.
2. It facilitates making colored tablets with a minimum of coloring substance.
3. It, in many instances, aids in the swallowability of a tablet.
4. It masks taste.

The manufacturing methods for coating will be touched on only briefly, when necessary. The reader is referred to the texts listed in the *Recommended Reading* section at the end of the chapter.

27.1. SUGAR COATING

Sugar coating is the oldest of the coating methods, and its use is much less common nowadays than a half a century ago, when all coating was carried out in this fashion.

The process of tablet coating will not be covered here, except to the extent of a brief overview.

The finished product has the overall composition shown in Fig. 27.1.

It is obvious from the figure that there is a series of steps necessary to carry out the operation. This process, in turn, is lengthy. It is traditionally done in coating pans. Solutions and syrups are added in just sufficient portions to make the tablets turn over, and the water is then evaporated off with hot air blasts. Once dry, one more application is added, dried, and so on.

Operator skill is necessary, in particular when pan coating is resorted to. Operational variables may be minimized by spray rather than ladling systems, but even so, much care is needed.

A more controlled system is provided by fluidization and spray application (Wurster apparatuses).

There are still several popular products on the market that are sugar-coated (ibuprofen products), but many popular products in today's marketplace that were once sugar-coated and are now film-coated (e.g., One-A-Day vitamins).

27.2. ORIGIN OF FILM COATING: ORGANIC SOLVENT COATING

In film coating a thin, polymeric film, usually with a thickness of 10–100 μm , is deposited on the surface of a tablet. The film consists of polymer, plasticizer, opacifier, and coloring agent. The method of deposition consists of dissolving or dispersing the ingredients in a suitable solvent (which, as shall be seen later in the chapter, may be water), and spraying the liquid onto the tablets, either in a coating pan or in a column.

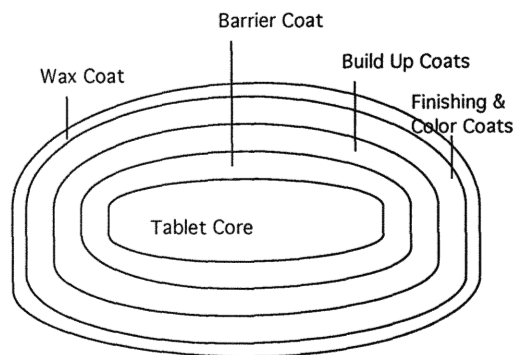


Fig. 27.1 Schematic of sugar-coated tablet.

The purpose of the film is (a) esthetic (Rowe, 1983, 1985); (b) protective; or (c) sustaining. The latter will be dealt with in a special section of the chapter. The manner in which it acts (delays) is either by dissolution or erosion of the polymer, osmosis, or drug diffusion. Requirements for an ordinary film coat are described, for instance, in a patent by Pital (1969).

A film coats tablets to form a membrane which is semi-permeable to water thereby permitting the tablet to disintegrate in two or three minutes after administration. Yet, the coating on the tablet gives excellent protection against external media. The dual characteristics are achieved by the combination in a coating composition of a film-forming water soluble solid, a water soluble polyglycol of high molecular weight.

Requirements for a good film is that (a) the film be uniform, (b) that it be without cracks, (c) that it adheres well to the tablet, (d) that it has no cracks or flaws in appearance (onionskin appearance). For engraved tablets, the grooves may not be "filled in."

As the solvent evaporates there will be a shrinkage. There is, furthermore, a difference in thermal expansion and contraction of the substrate and the film. To withstand both of these vicissitudes, the film must possess strength and elasticity. For most applications, insoluble fillers (opacifiers such as titanium dioxide) are detrimental, because they reduce the cross section of intact film. Some (e.g., talc), however, have the capability of reducing the stress buildup; hence, the film is not as likely to crack.

27.3. ENTERIC COATINGS

Coatings that resist dissolution in the gastric fluids, but disintegrate or dissolve in the small intestine are often denoted *enteric coatings*. They are insoluble in acid and soluble in alkali, and as such, they contain carboxyl (or other acidic) groups. A list of such polymers is shown in Table 27.1.

Enteric films may be used simply as the barrier coat in a sugar-coated tablet.

27.3.1. Defects

Two common types of defects in film coating are peeling and edge splitting. Bridging and covering over of the intagliation is also a problem. These are exemplified in Fig. 27.2.

Table 27.1 Enteric Polymers

Polymer	Name in trade	pH range if soluble
Cellulose acetate phthalate	CAP	> 6.0
HPMC phthalate	HP50	> 5.0
Polymethacrylic acid, ethyl acrylate	Eudragit L30D	> 5.5
Polymethacrylic acid	Eudragit L	> 5.5
Polymethacrylic acid, methylmethacrylate Shellac	Confectioner's glaze	> 6.0

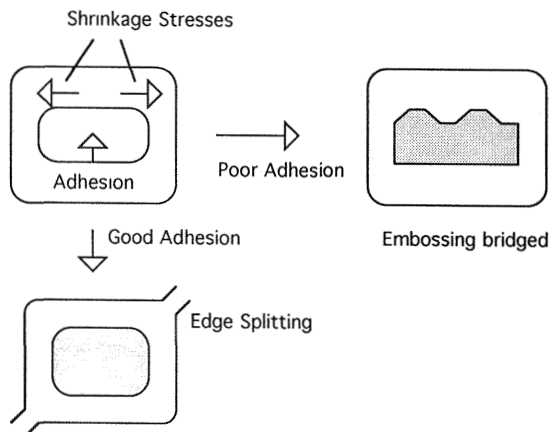


Fig. 27.2 Defect types in film-coated tablets.

Splitting can occur over the dome of the tablet or (more often) at the edges, where it is denoted edge-splitting. Defect rates of this type are a function of the molecular weight of the polymer used. Rowe (1980) reported on the effect of the molecular weight of hydroxypropyl methylcellulose (HPMC) on the percentage of edge-splitting in film-coated tablets.

The foregoing types of defects may be problems with the film (plasticizer), but may equally well be manufacturing problems. Discussion of manufacturing conditions is, as mentioned in the preface, not the intent of this text, but it should be mentioned in this connection that spraying at too high a rate, or by using insufficient inlet air, and having the tablet mass at too low a temperature cause defects known as “pickers.” The tablets will stick together for a short while and then separate and, in doing so, a small amount of film is removed. This is particularly important in sustained-release films, because such a pick causes dose-dumping.

The incidence of bridging (obliteration of the embossing) will be discussed further in the following, but contributors are the plasticizer and the concentration of plasticizer.

The thickness of the film coat affects emboss-obliteration, and this problem has been addressed by Rowe (1982a,b), who coated tablets with varying amounts of a 5% w/v solution of HPMC in water, using glycerin (in an amount of 20% of the HPMC) as plasticizer.

The residual stresses in films caused by shrinkage are smaller in thin films, and this trend continues until a limiting value is reached (Meissner and Baldauf, 1951; Gardon, 1967). The intrinsic adhesion, however, at the film–tablet interface, remains constant and independent of thickness. Therefore, it follows that thin films will be predominated by adhesive forces, which means that the embossing will not coat over. The opposite is true for thick films, up until a point where the embossing completely disappears from view. Figure 27.3 demonstrates the effect of film thickness (μm) on the percentage occurrence of defects.

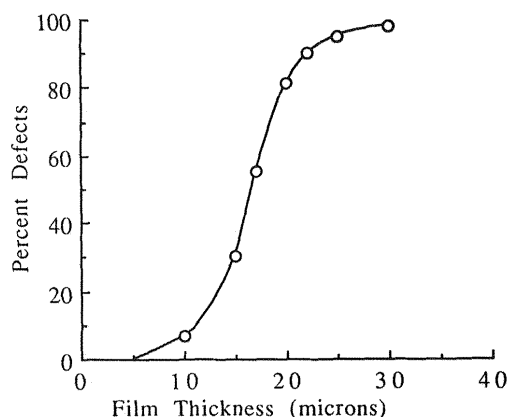


Fig. 27.3 The effect of the thickness of EC films on the occurrence of defects in film coating. (Data from Rowe, 1980.)

27.4. PLASTICIZERS

Plasticizers, as mentioned in Chap. 26, have the capability of reducing the glass transition temperature of a film (Rowe 1982 a,b) (i.e., the polymer is more likely to be in the rubbery—a plastic—state). Plasticizers include castor oil, diethyl succinate, and polyethylene glycols (PEGs). The effect of various plasticizers on a methyl cellulose film is shown in Table 27.2.

There is *some* sense in considering the mechanical effect that a plasticizer has (e.g., the effect on the end use of the film; that is, its suitability for tablet coating). To this end some investigators use tensile strength and yield point as indicators, but it is seen from the table that the two criteria would lead to different conclusions, because the yield point decreases in the series, but the tensile strength does not.

More to the point, is the effect that plasticizers have on the glass transition (T_g) values of polymers, for T_g depends on chain mobility, and the purpose of a plasticizer is to improve the chain mobility.

The measurement of T_g of plasticized films by differential scanning calorimetry (DSC) and by thermal gravimetric analysis (TGA) is complex, and the use of the braided torsion balance (BTB) is a preferred method. If such instrumentation is not available, the value of T_g for a plasticized polymer may be estimated by knowledge

Table 27.2 Properties of Plasticized Methylcellulose Films (Containing 30% Plasticizer)

Plasticizer	Tensile strength (MPa)	Yield point (MPa)	Ultimate elongation (%)
None	70	59	14
PG	35	33	50
PEG 6000	44	22	39
Glycerin	46	14	48

Source: Greninger and Savage, 1959.

of the T_g values for the individual components by using the formula by Kelley and Bueche (1961):

$$T_g = \{\beta_p T_{gp} \phi_p - \beta_d T_{gd}(1 - \phi_p)\} / \{\beta_p \phi_p - \beta_d(1 - \phi_p)\} \quad (27.1)$$

where the subscripts p and d denote “polymer” and “plasticizer,” and where β is the volumetric expansion coefficient (of the order of $5 \times 10^{-4}/^\circ\text{C}$), and ϕ_p denotes volume fraction of polymer.

Table 27.3 shows the effect of concentration and nature of plasticizer concentration on T_g values of hydroxymethyl propylcellulose (HPMC) film coatings.

The functional effect of plasticizer concentration on T_g values of polymer films has been reported by Entwistle and Rowe (1979).

In Fig. 27.4, there is a maximum in intrinsic viscosity. It so happens that this corresponds to the minimum in a series of properties (elongation at rupture, work done to produce failure, and tensile strength). This is demonstrated in Fig. 27.5 for the tensile strength, but a similar plot emerges when work at failure and elongation at rupture are plotted versus molecular weight. The plot in Fig. 29.5 is represented in log-log form, simply for presentation convenience.

27.5. GLASS TRANSITION TEMPERATURES

Previous chapters have shown that the predominant method for determining glass transition temperature is differential scanning calorimetry. The peaks for such transitions are weak and, for films, a better method exists; namely, the torsional braid pendulum. Sakellariou et al. (1985) have compared T_g values obtained by DSC, TGA, and torsional braid pendulum (TBP). The comparison of data is listed in Table 27.4.

27.6. STRENGTH OF FILMS AND EFFECT OF STORAGE

Rowe (1982a), based on work by Sato (1980) and Chow (1976), considered the strain induced during storage of a film-coated tablet, and assumed that there is an isotropic linear strain ε , of

Table 27.3 Effect of Plasticizers and Their Concentration on T_g Values of HPMC Films and Effect on Bridging

Plasticizer	Concentration (W%)	T_g (C)	Bridging incidence (%)
None	0	177	97
PG	10	141	91
PG	30	75	87
PEG 200	10	140	73
PEG 200	30	70	26
Glycerin	10	153	24
Glycerin	30	103	22

Source: Entwistle and Rowe, 1979; Rowe and Forse, 1981.

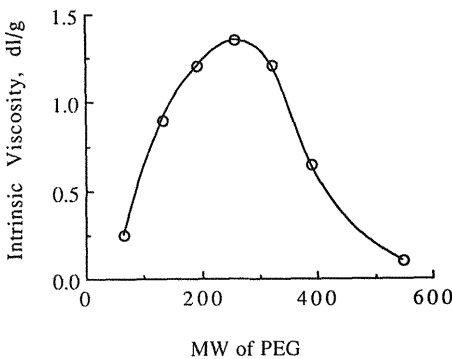


Fig. 27.4 Effect of molecular weight of plasticizer on intrinsic viscosity of HPMC. (Data from Entwistle and Rowe, 1979.)

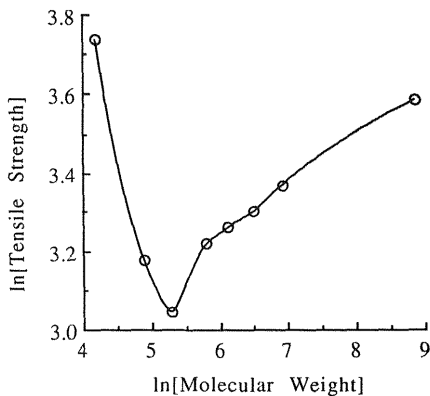


Fig. 27.5 Tensile strength of HPMC films as a function of molecular weight of PEG. (Data from Entwistle and Rowe, 1979.)

Table 27.4 Comparative Values for T_g by Different Methods

Polymer	T_g by DSC	T_g by TGA	T_g by TBP	Literature Ref.
CAP	171	170	185	Porter and Ridgeway, 1983
HP50	146	146		
HP55	136	133		
EC	133	133	129	Entwistle and Rowe, 1979
HPMC	180	169–174	177	Entwistle and Rowe, 1979
			155	Okshmafe and York, 1985

$$\varepsilon = \Delta V/3V \quad (27.2)$$

From this and the assumption that the strains in the coating and substrate at corresponding points are identical (Stanley et al., 1980), Rowe arrived at the following formula for the stress in the film:

$$P = \{E/(1 - \nu)\}[\Delta V/3V] \quad (27.3)$$

where ν is the Poissons ratio, E is the Young's modulus, and ΔV is the volume increase of a tablet, of original volume V , on storage. Rowe (1982) gives an example for a film with an E value of 10^3 MPa and $\nu = 0.35$. In such a case, a 1% volume increase in storage of a tablet would result in $P = 5.1$ MPa, whereas a 10% increase in volume would yield $P = 51$ MPa. This latter is close to the tensile strength of most films. Often directly compressed tablets expand to such an extent on moist storage (Sangekar et al., 1972), in particular owing to slow expansion caused by moisture uptake of the disintegrant.

27.7. SOLVENT SYSTEM

The solvent used is of importance in that it governs the shrinking stresses, because the concentration at which gelling takes place is governed by the solvent and (in a kinetic sense) the rate of evaporation. For aqueous film-coating the solvent is essentially fixed, but as some film-coating is still carried out with solvents, a word and two about this point may be in order.

According to the Hildebrand-Scott theory (Hildebrand and Scott, 1950), the enthalpy of mixing ΔH is given by

$$\Delta H = V_m \{(\Delta E_1/V_1)^{0.5} - (\Delta E_2/V_2)^{0.5}\}^2 \phi_1(1 - \phi_1) \quad (27.4)$$

where V_m is the volume of the final mixture, ΔE_1 and ΔE_2 are the vaporization energies of the two components, V_1 and V_2 are the molar volumes of each component and ϕ_1 is the volume fraction of component "1." It is customary to denote the term

$$\{(\Delta H - RT)/V\}^{0.5} = \delta \quad (27.5)$$

the solubility parameter. However, in the solubility parameter definition [see Eq. (27.5)] ΔH is the heat of evaporation. The heat of mixing, ΔH , in Eq. (27.4) is taken to be a function of $(\delta_1 - \delta_2)^2$. For cases where $\delta_1 = \delta_2$ there is complete miscibility, complete solubility. In this manner, it is possible to assess the compatibility between two polymers. There are lists of vaporization heats of solvents published (e.g., Burrell, 1975), so that for the solvents used, the calculation of δ values can be carried out. Burrell (1975) describes a method for calculating the values of the solubility parameter for polymers. By this method, a polymer in a certain concentration is observed in three solvents exhibiting "poor," "moderate," and "strong" hydrogen bonding. The solubility of the polymer in the three solvents is assessed (e.g., by clarity, absence of lumps), and if the polymer is soluble in one, but not in the other two, then that is assumed to be its solubility parameter. If it is soluble in more than one, then the assessed solubility parameter is the midpoint between the solubility parameters of the two or three solvents. Crude as the method may seem, it seems to give good qualitative results. Tables 27.5 and 27.6 show examples of this.

Table 27.5 δ -Values for EC

EC-grade	Solvent having poor H-bonding	Solvent having moderate H-bonding	Solvent with strong H-bonding
T-10	17.4–19.5	16.0–20.2	19.4–23.4
N-22	16.6–22.6	15.1–22.1	19.4–29.7
K-200	17.4–19.4	17.4–22.1	19.4–23.3

The method, when used for three EC-grades worked well with three solvents. For instance, the N-grade of EC has a δ -value of $19 \text{ MPa}^{1/2}$. This value is within the intervals shown in the second line of Table 27.5. Table 27.6 shows that the tensile strength and the Young's modulus decrease as the δ -value of the solvent used for casting the film decreases. It is noted that the data for elongation (last column in Table 27.5) do not show a consistent trend.

To improve on the picture just presented, some authors (Cowley et al., 1966; Hansen, 1967) have suggested constructing three-dimensional solubility plots. These, however, are difficult to apply to formulation practices.

27.8. AQUEOUS FILM COATING

Film coatings were, in their early development applied using a solvent, but environmental regulations are now such that virtually all coatings are made by water-soluble polymers.

Here, hydroxypropyl methylcellulose (HPMC) or hydroxypropylcellulose (HPC) with plasticizers have been polymers of choice. Eudragits have also found wide use. For the latter, Felton and McGuinity (1996, 1997) report the use of Eudragit L 30 D-55, plasticized with triethyl citrate, tributyl citrate, dibutyl sebacate, or PEG 6000.

To evaluate the suitability of films, researchers have used the butt adhesion technique and the peel test, which determine the force that is needed to separate a polymer film from a substrate surface (Fung and Parrott, 1980; Fisher and Rowe, 1976; Johnson and Zografi, 1986).

Felton and McGuinity (1996, 1997), Wang et al. (1996), and Felton et al. (1996) have described techniques, whereby the edge of a film on a tablet is just lifted,

Table 27.6 Solvent Effects on Properties of EC N-Grade Films

Solvent	δ -value, ($\text{MPa}^{0.5}$)	Young's modulus (MPa)	Tensile strength (MPa)	Elongation (%)
Chlorobenzene	1.52	1689	51.8	25.0
2-Nitropropane	1.35	1627	51.2	26.7
Benzene	1.57	1868	59.0	33.8

and attached to an instrumented platen that may be raised. The deflection is monitored as a function of force, and a plot, such as shown in Fig. 27.6, is obtained. The hydrophobicity of the surface influenced the adhesion when the plasticizer was water-soluble, but not when it was water-insoluble.

27.9. PROPERTIES OF AQUEOUS FILMS

Rowe (1976) has studied the effect of the molecular weight of HPMC on the properties, such as continuity of film, hardness, elasticity, and substrate-to-film adhesion, of films made from HPMC.

Not unexpectedly, the *Young's modulus* increases with molecular weight, and the plot is linear (Fig. 27.7). Other characteristics are functions of the molecular weight of the film polymer. *Brinell hardness* (Fig. 27.8) is a linear function of the molecular weight. *Crushing strength* is shown in Fig. 27.9 as being a linear function

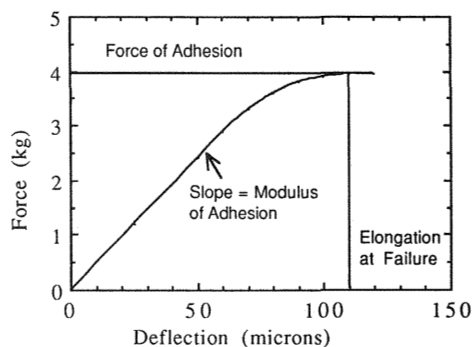


Fig. 27.6 Peel test to determine the force needed to separate a polymer film from a substrate surface. (Data from Felton and McGinity, 1997.)

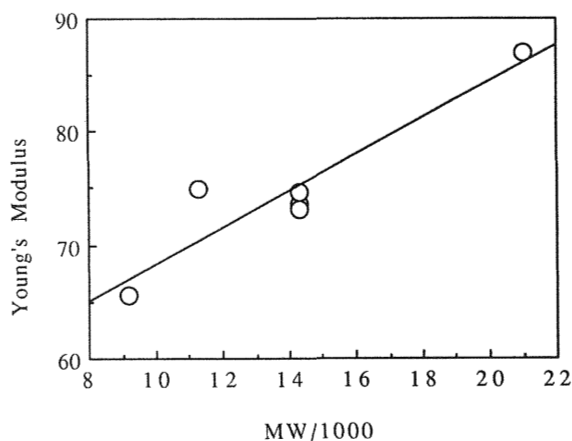


Fig. 27.7 Young's modulus as a function of molecular weight of film polymer. (Data from Rowe, 1976.)

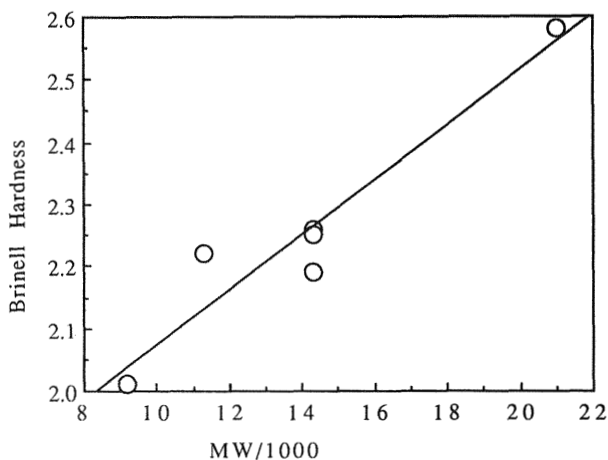


Fig. 27.8 Brinell hardness as a function of the molecular weight of a film polymer. (Data from Rowe, 1976.)

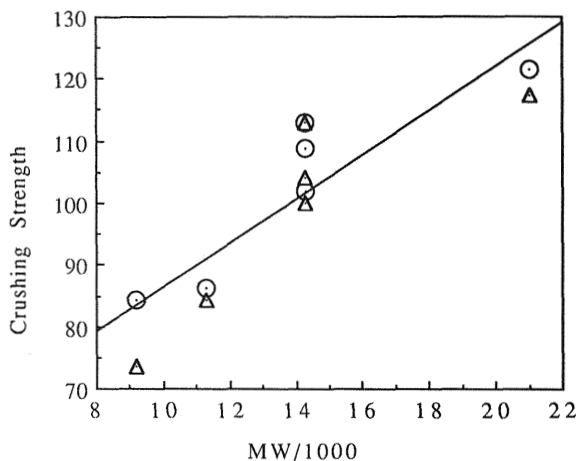


Fig. 27.9 Crushing strength as a function of a polymer's molecular weight. Circles are 6.5 mm tablets and triangles are 8.5 mm tablets. (Data from Rowe, 1976.)

of molecular weight, but the plot may be curved and asymptote. The *percentage of tablet defects* (as judged by mercury penetration) in particular batches of film-coated tablets is loglinearly decreasing with molecular weight (Fig. 27.10).

27.10. SUSTAINED-RELEASE COATINGS ON TABLETS

It is obvious, from the foregoing discussion, that film coating should be capable of being used as sustained-release mediators. Lindahl (1986) has described a sustained-release-coated tablet "comprising a drug-containing tablet and a coating or mem-

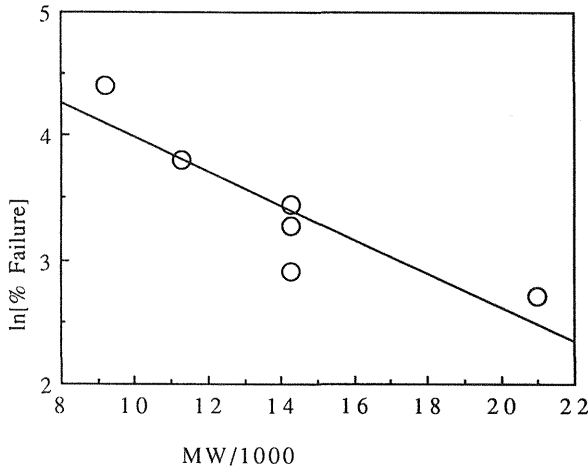


Fig. 27.10 Percentage of tablets failing mercury penetration test for continuity of film. Data from three tablet sizes are averaged. (Data from Rowe, 1976.)

brane surround[ing] the same, wherein the coating...is water-insoluble and insoluble in gastrointestinal fluids and consist[s] essentially of a terpolymer of polyvinylchloride, polyvinylacetate and polyvinylalcohol and a water-soluble pore-creating substance....”

Polli (1970) describes a similar principle in which CAP or nitrocellulose are the film formers, castor oil and PG the plasticizer, and acetone the solvent.

Ethyl cellulose (EC) films have been used in this type of sustained-release coatings. The concentration of plasticizer in such instances would be of importance. Rowe (1985) has shown the effect of plasticizer (here, HPMC) in ethyl cellulose-coated tablets (Figs. 27.11 and 27.12).

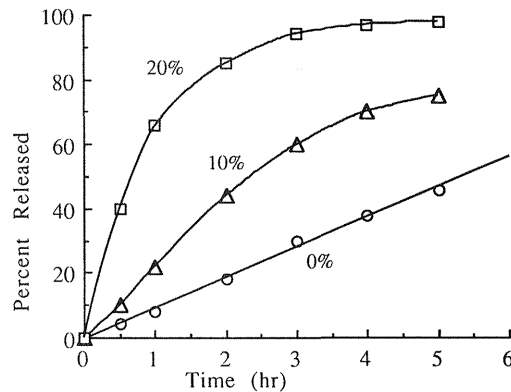


Fig. 27.11 Effect of plasticizer level (% HPMC) on release of drug from an EC film-coated tablet. (Data from Rowe, 1985.)

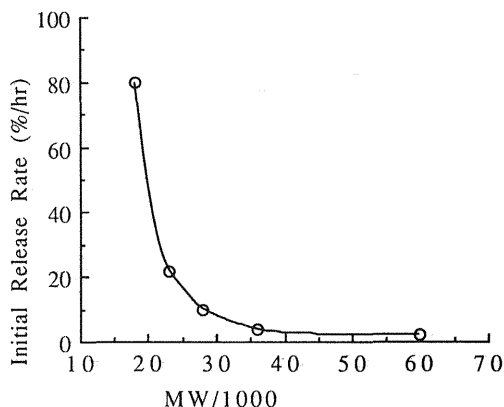


Fig. 27.12 Effect of MW of EC on the initial release from a film-coated tablet with sustaining properties. (Data from Rowe, 1985.)

SYMBOLS

E = Young's modulus

EC = ethyl cellulose

ΔE_1 = vaporization energies of component 1

ΔE_2 = vaporization energies of component 2

MC = methylcellulose

PG = propylene glycol

PEG = polyoxyethylene glycol

HPMC = hydroxypropyl methylcellulose

ΔH = (a) $V_m\{(\Delta E_1/V_1)^{0.5} - (\Delta E_2/V_2)^{0.5}\}\phi_1\phi_2$; (b) heat of mixing; (c) heat of evaporation

P = stress in film

T_g = glass transition temperature

T_g = glass transition temperature of polymer

T_{gp} = glass transition temperature of plasticizer

V_1 = molar volume of component 1

V_2 = molar volume of component 2

β_p = volumetric expansion coefficient of polymer

β_d = volumetric expansion coefficient of plasticizer

δ = solubility parameter

ϕ_p = volume fraction of polymer

ϕ_1 = volume fraction of component 1

ν = Poisson's ratio

REFERENCES

- Burrell H (1975). In: Bandrup J, Immergut EH, eds. *Polymer Handbook*, 2nd ed. Wiley Interscience, New York, pp IV, 337.
- Chow TS, Liu CA, Penwell RC (1976). *J Polym Sci Polym Phys Ed* 14:1311.
- Entwistle CA, Rowe RC (1979). *J Pharm Pharmacol* 31:269.

- Felton LA, McGinity JW (1996). *Pharm Dev Technol* 1:381.
- Felton LA, McGinity JW (1997). *Int J Pharm* 154:167.
- Felton LA, Shah NH, Zhang G, Infeld MH, Malick AW, McGinity JW (1996). *Int J Pharm* 127:203.
- Fisher DG, Rowe RC (1976). *J Pharm Pharmacol* 28:886.
- Fung RM, Parrott EL (1980). *J Pharm Sci* 69:439.
- Greminger GC, Savage AB (1959). In: Whistler RL, ed. *Industrial Gums—Polysaccharides and Their Derivatives*. Academic Press, New York, pp 565–596.
- Gardon JL (1967). In: *Treatise on Adhesion and Adhesives*, vol 1. Marcel Dekker, New York, pp 269–324.
- Hansen CM (1967). *J Pain Technol* 39:104.
- Johnson BA, Zografi G (1986). *J Pharm Sci* 75:529.
- Kelley FN, Bueche F (1961). *J Polymer Sci* 50:549.
- Lindahl AR, Erlandson SAB (1986). U. S. patent 4,629,620.
- Meissner HP, Baldauf GH (1951). *Trans Am Soc Mech Eng* pp 697–704.
- Okshmafe AO, York P (1985). *Pharm Res* 2:19.
- Pital G (1969). U. S. patent 3,476,588, filed 1964.
- Polli GP (1970). U. S. patent 3,538,214.
- Porter SC, Ridgway K (1983). *J Pharm Pharmacol* 35:341.
- Rowe RC (1976). *Pharm Acta Helv* 51:330.
- Rowe RC (1980). *J Pharm Pharmacol* 32:584.
- Rowe RC (1982). *Int J Pharm Technol Prod Manuf* 3:3.
- Rowe RC (1982a). *J Pharm Pharmacol* 35:112.
- Rowe RC (1983). *Pharm Ind* 4:173.
- Rowe RC (1985). *Pharm Int Jan* p 14.
- Rowe RC, Forse SF (1981). *J Pharm Pharmacol* 33:174.
- Sakellariou P, Rowe RC, White EFT (1985). *Int J Pharm* 27:267.
- Sangekar SA, Sarli M, Sheth PR (1972). *J Pharm Sci* 61:939.
- Sato K (1980). *Prog Org Coat* 8:143.
- Stanley P, Rose RC, Newton JM (1981). *J Pharm Pharmacol* 33:557.
- Wang C–C, Zhang G, Shah NH, Infeld MH, Malick AW, McGinity JW (1996). *Pharm Dev Technol* 1:213.

RECOMMENDED READING

- Seitz JA, Mehta SP, Yeager JL (1986). In: Lachman L, Lieberman HA, Kanig JL, eds. *Theory and Practice of Pharmaceutical Technology*. 3rd ed. Lea & Febiger, Philadelphia, pp 346–373.

The development of sustained-release products has been ongoing in the pharmaceutical industry, ever since Smith Kline & French Laboratories marketed a sustained-release product in the early 1950s. The rationale for such a dosage form is self-evident: taking one or two doses a day is preferable to a patient over taking two to four doses daily.

There are several principles that have been developed over the years. Some of these consist of a singular-dosage form, acting in the sustained fashion, others are multiparticulate. It is the former that will be discussed first, and these are the following:

1. Complexation and derivatization
2. Erosion tablets
3. Rigid matrices
4. Swellable matrices
5. Floatable tablets
6. Osmotic pumps

28.1. CHEMICAL MODIFICATION

If a drug appears to require frequent dosing, then the problem is often one of solubility. If the drug substance is consistently absorbed throughout the entire (or a substantial part) of the gastrointestinal tract, then lowering its solubility will prolong the time it stays undissolved.

Ideally, in this manner the drug will be absorbed more slowly, over a longer period of time, and if the absorption is such, when a derivative with lower solubility is used, the therapeutic levels (ThL in Fig. 28.1) are reached over a longer time. Then, there is the dual benefit of (a) reduced risk of reaching the toxic limit (TL), and (b) prolonged action. Such products can, in principle, be administered as rapidly disintegrating tablets or capsules.

For a variety of reasons, a linear, in vitro release pattern is preferable, and this is the goal of most sustained-release formulation efforts.

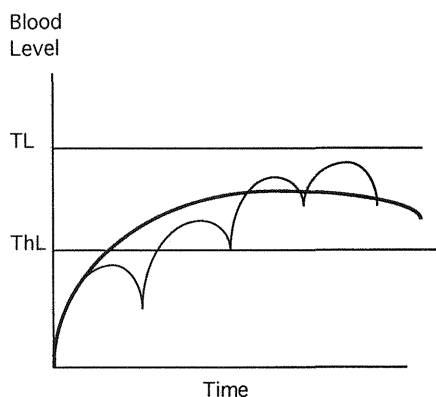


Fig. 28.1 Schematic of sustained release.

28.2. ENTERIC COATING

Historically, the earliest attempts at sustained-release dosage forms by manipulation of the dosage form was in the form of enteric-coated tablets (Fig. 28.2). This is a bimodal approach, in that some of the dosage form (in the sugar coat of a tablet) will release immediately, some of it (in the enteric-coated core) will not release until the tablet has passed into the small intestine where the enteric coat may dissolve.

In vitro testing of such products are most often carried out by a so-called half-change method. The tablet is subjected to N/10 hydrochloric acid for 30 min–1 h, and the dissolution medium is then changed to a pH 7 buffer.

Products of this type are difficult to make consistently, integrity of the enteric coat being difficult to achieve in scaled-up manufacture. The gastric-emptying time is also a disadvantage, because the release depends on the product staying in the stomach for a certain length of time, and then passing into the small intestine. The bimodal nature, in itself, is also a disadvantage, and more continuous-release patterns are of advantage.

28.3. EROSION TABLETS

Erosion tablets are tablets that do not disintegrate, but simply erode, as time in contact with dissolution medium progresses. Carstensen and Valentine (1966) found this to hold true and used carnauba wax in which they imbedded the drug substance. To control the rate of erosion, controlled amounts of polyethylene glycol distearate were added. Sterotex (hydrogenated vegetable oil) has also been used as a wax base.

Some grades of hydroxypropyl methylcellulose (HPMC) form matrices that, in part, behave similar to erosion tablets (Christenson and Dale, 1966; Lapidus and Lordi, 1966, 1968; Ford et al., 1985a,b,c, 1987).

Erosion tablets often follow a cube-root equation. The solid “sloughs off” at a constant rate; that is,

$$da/dt = -K \quad (28.1)$$

where a is the “diameter” of the tablet (assumed spherical), t is time, and K is an erosion constant. This integrates to

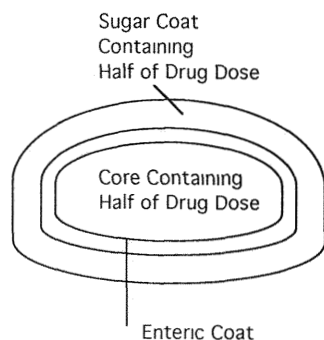


Fig. 28.2 Principle of sustained release based on enteric coating.

$$a = a_0 - Kt \quad (28.2)$$

or

$$1 - (a/a_0) = (K/a_0)t \quad (28.3)$$

and since the tablet is considered spherical, its volume v is

$$v = (\pi/6)a^3 \quad (28.4)$$

or

$$a = (6v/\pi)^{1/3} \quad (28.5)$$

hence,

$$a/a_0 = \{v/v_0\}^{1/3} = \{m/m_0\}^{1/3} \quad (28.6)$$

where a_0 is the original diameter of the tablet, m is mass not dissolved, and m_0 is the original mass of the tablet. Inserting this in Eq. (28.3) gives:

$$1 - (m/m_0)^{1/3} = (K/a_0)t \quad (28.7)$$

Equation (28.7) is followed in a wax matrix system, except there is a lag time, because of initial wetting of the tablet surface.

Christenson and Dale (1966) find a linear erosion pattern as described in Eq. (28.2).

Even though wax tablets are not porous per se, there is always some residual porosity. This may, to some degree, invalidate equations such as Eq. (28.2). HPMC, as shown in Fig. 28.3, exhibits an eroding front which, in the case of certain eroding matrices, is actually not linear, but square-root in time.

If this is true, Eq. (28.2) takes the form

$$a_0 - a = \phi\{t - t_i\}^{1/2} \quad (28.8)$$

where t_i is a lag time, and ϕ is a square-root constant. By dividing through by a_0 and following a development akin to Eqs. (28.8) and (28.7) this now becomes

$$1 - (m/m_0)^{1/3} = (\phi/a_0) \{t - t_i\}^{1/2} \quad (28.9)$$

Even with erosion tablets there will be some intrusion of liquid into the matrix. This is presumably the manner in which the sloughing off of the surface occurs.

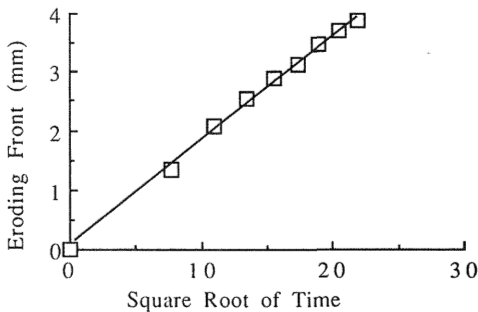


Fig. 28.3 Eroding front for HPMC matrix. (Data from Konrad et al., 1998.)

From a theoretical point of view (Carstensen, 1980), the intrusion of a liquid front into a (porous) matrix should follow the Washburn equation (Washburn, 1921; Nogami et al., 1966; Couvreur, 1975):

$$dL/dt = -Qr^2/(8\eta L) = -q/L \quad (28.10)$$

where

$$q = Qr^2/(8\eta) \quad (28.11)$$

and where L is the length of the intrusion at time t , r is the average radius of the pores, η is the viscosity of the liquid, and Q is a constant.

If Eq. (28.9) holds, then the linear erosion would presumable be related to L ; that is,

$$L = \beta(a_0 - a) \quad (28.12)$$

so that

$$dL/dt = -\beta(da/dt) = -q\beta(a_0 - a) \quad (28.13)$$

so that by integration

$$-\ln[1 - (a/a_0)] = qt - \Omega \quad (28.14)$$

or

$$\ln\{1 - (m/m_0)^{1/3}\} = -qt + \Omega \quad (28.15)$$

where Ω is an initial condition constant related to the fact that wetting of the tablet surface requires a small, yet measurable, length of time.

Other recession relations exist; for instance, Bamba et al. (1979) have shown that in certain gums the erosion front itself follows a cube-root law.

28.4. MATRIX SYSTEMS

A *matrix* is a uniform mixture of drug, excipients, and (e.g.) polymer that is homogeneously fixed in a solid dosage form (Dow Methocel Bulletin, 1982).

The basic principle of a rigid matrix was first developed by Higuchi (1963), and the aspects of it are depicted in Fig. 28.4.

A two-dimensional model is described here, as it illustrates the limitations and some of the misconceptions of the model in past literature.

The drug substance, which has a solubility in the dissolution medium of $S \text{ g/cm}^3$, is dispersed in the matrix, which is insoluble in the dissolution medium. The concentration of drug in the matrix is $A \text{ g/cm}^3$ of matrix. The matrix is porous, with a porosity of ε . Liquid will intrude from the bulk liquid, and in the model presented here will enter from the right in Fig. 28.4. The rate and extent of intrusion will follow Eq. (28.10), so that there will be a liquid front, as shown in the figure, which is $x = L \text{ cm}$ from the surface (where $x = 0$) at time t .

The intruding liquid will dissolve drug substance, and at a given level of intrusion L , part of the matrix, between L and h , will still contain solid particles that are not yet completely dissolved, whereas in the volume to the right of h (i.e., for $0 < x < h$) all particles are dissolved. In the volume $L > x > h$, the liquid will be saturated in drug substance, but when $x < h$, the concentration steadily decreases

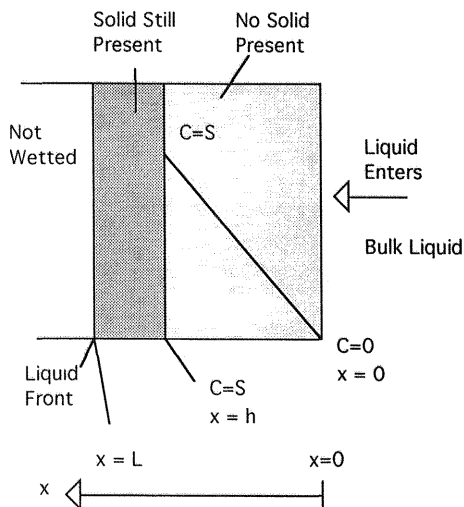


Fig. 28.4 Schematic of a rigid matrix in two dimensions with one side (to the right) exposed to liquid.

until it is zero at the interface with the bulk liquid. It is, as shown in the figure, assumed that Fick's law applies, which will make the concentration gradient constant (i.e., the concentration will be linear in distance up until $x = L$).

The volume of liquid in the volume $0 < x < L$ is $h\varepsilon$ and the average concentration is $0.5S$, so that the amount of drug present in the volume at time t is $0.5S\varepsilon h$. The amount of material Q , released at time t , will be the amount originally present in this volume (Ah), less what is present at time t ; that is,

$$Q = Ah - 0.5S\varepsilon h \quad (28.16)$$

which in differential form is

$$dQ/dt = \{A - 0.5S\varepsilon\} dh/dt \quad (28.17)$$

Considering the amount in the liquid present at $x = h$ to be $S\varepsilon$, then the concentration gradient (see Fig. 28.4) is $S\varepsilon$ in the region $0 < x < h$. Fick's law then gives

$$dQ/dt = DS\varepsilon/h \quad (28.18)$$

where D is the diffusion coefficient.

Combining Eq. (28.16), (28.17), and (28.18) now gives

$$dh/h = \{DS\varepsilon/[A - 0.5S\varepsilon]\} dt \quad (28.19)$$

which may be integrated to

$$0.5h^2 = \{DS\varepsilon/[A - 0.5S\varepsilon]\} t \quad (28.20)$$

where $t = 0$ implies $h = 0$ so that initial conditions are met. Introducing Eq. 28.6 this becomes:

$$Q = \{2DS\varepsilon[A - 0.5S\varepsilon]\}^{1/2} t^{1/2} \quad (28.21)$$

The domain of this equation is $A > 0.5S\varepsilon$. If this does not apply, then the equation becomes (Fessi et al., 1982)

$$Q^2 = a^2 Dt \quad (28.22)$$

where a is the area through which the diffusion can take place.

There are two limiting concepts in this model, and this type of preparation:

1. The matrix must be "continuous."
2. The pore space must be "continuous" (i.e., pores that are occluded will not work in the model).

The limiting situations are then (a) when the drug content is very low and (b) when the matrix material content is very low. These two situations will be dealt with at a later point in this section.

A couple of points are of importance. The porosity term in Eq. (28.21) is *not* the porosity, $\varepsilon_{\text{tablet}}$ of the original tablet, but rather, the porosity ε in the volume $0 < x < h$. This consists of the tablet porosity ε_t , plus the porosity ε_d , created by the complete dissolution of the drug substance in the volume. This latter is

$$\varepsilon_d = A/\rho_A \text{ cm}^3 \quad (28.23)$$

where ρ_A is the particle density of the drug substance; that is,

$$\varepsilon = \varepsilon_t + A/\rho_d \quad (28.24)$$

This is a means of controlling (increasing) the dissolution rate of the drug by adding soluble excipients (e.g., lactose). If they are present in a concentration of $B \text{ g/cm}^3$, then the porosity to be used in Eq. (28.21) would be

$$\varepsilon = \varepsilon_t + A/\rho_A + B/\rho_B \quad (28.25)$$

where ρ_B is the particle density of the soluble excipient. Conversely if it is desired to decrease the dissolution rate, then a larger ratio of matrix to drug substance (a decrease in A) would be called for.

The difference between Eqs. (28.21) and (28.22) deals with the fact that below a certain porosity, the pore space is no longer continuous. This aspect is the subject of percolation theory.

28.5. PERCOLATION THEORY

Percolation theory is a mathematical tool, that allows prediction of the foregoing situations [i.e., whether Eq. (28.21) or (28.22) applies]. It has been dealt with by several authors (Leuenberger et al., 1987, 1995; Adrover et al., 1996; Fernandez-Hervas et al., 1995, 1998; Towgen and Biglin, 1998).

For liquid intrusion (transport) to occur, it is necessary that "clusters" occur and that there are sites or bond percolation that take place (Stauffer and Aharoni, 1985). A continuous pathway of sites that "conduct" (percolation sites) must exist in the matrix. When the (tablet) porosity is very low, then the number of conducting sites will be so low that a continuous pathway will not occur. The porosity at which this occurs is denoted the critical percolation threshold (ε^*). Above this there will be a part of the pores that are available for intrusion, and this is designated the accessible fraction (ε_a), and the total porosity (ε) is the sum of these two. Hence,

$$\varepsilon_a = (\varepsilon - \varepsilon^*)^\beta \quad \varepsilon > \varepsilon^* \quad (28.26)$$

$$\varepsilon_a = 0 \quad \text{when } \varepsilon < \varepsilon^* \quad (28.27)$$

Here, β is a constant of universal nature. In percolation theory, $\beta = 0.3$ – 0.4 for real systems. (For two-dimensional systems, $\beta = 0.14$).

In general, diffusion is defined by flux J (i.e., amount dissolved by surface area).

$$J = -D_b(dC/dx) \quad (28.28)$$

where C is concentration, x is distance, D is diffusion coefficient, and D_b is the bulk diffusion coefficient at steady state. In percolation theory, the concept of the dimensionless quantity D , given by

$$D = D_b/D_a \quad (28.29)$$

is introduced. D_a is the aqueous medium diffusion coefficient (Stauffer and Ahorony, 1985). These authors showed that

$$D = D_b/D_a = \mu(\varepsilon - \varepsilon_c)^\phi \quad (28.30)$$

where μ is a system-dependent constant, and ϕ is a universal constant that has the value 2.0 for three-dimensional matrices.

The fraction of drug, denoted A (g/cm³), becomes the porosity ε_d , in the exhausted part of the matrix, and Eq. (28.23) may be written

$$A = \varepsilon_d \rho \quad (28.31)$$

The total porosity ε of the matrix mixture, hence, becomes

$$\varepsilon = \varepsilon_d + \varepsilon_i \quad (28.32)$$

where ε_i is the tableted porosity (i.e., the porosity before dissolution). The square-root law, under these circumstances becomes

$$Q = \{[D_e \varepsilon S[2\varepsilon_d \rho - \varepsilon S]t]\}^{1/2} \quad (28.33)$$

where D_e is the effective (traditional) diffusion coefficient of the drug substance in the medium within the pores. This term is a function of the tortuosity τ and, according to the theory of percolation (Siegel, 1986),

$$D_b = D_a \varepsilon^a / \tau^2 \quad (28.34)$$

There is a substantial tortuosity effect at low drug loadings, but at higher drug loadings it becomes close to unity, so that its effect may be neglected. Towgen and Binglin (1998) have reported tortuosities at various loadings of hydrocortisone, loaded into polyethylene–vinyl alcohol (EVAL) matrices and found that above a loading of 11% the tortuosity becomes 3 or less.

Domb (1983), suggests that, in a lattice, the sites can be either occupied by A component or B component, and where the A threshold depends on (a) what type of lattice is created, and (b) at which concentration of B this substance is dominant in the system B/A or vice versa.

Caraballo et al. (1996) and Milán et al. (1998) have shown that there is a linear relation between the particle size in matrix tablets and the drug percolation threshold; in these studies, they used KCl and caffeine as model drugs.

Domb (1983) has reported work on percolation threshold in Eudragit RS-PM matrices. The Leuenberger-Bonnie equation may be written

$$\beta = c(\varepsilon - \varepsilon_c) \quad (28.35)$$

where β is the slope of the Higuchi plot, ε is total porosity (including porosity created by dissolution of drug and excipients), and ε_c is the threshold porosity. Therefore, it should be possible to plot the slope of the Higuchi plots versus total porosity and determine the critical porosity by the x -axis intercept.

That this is so is exemplified in Fig. 28.5. The figure shows that the threshold porosity is (intercept/slope)

$$\varepsilon^* = 0.11181/1.461 = 0.076 \quad (28.36)$$

28.6. COMPLEXATION BETWEEN DRUG AND POLYMER

As will be seen in the following, most sustained-release products are based on the use of polymers of high molecular weight. It should be pointed out at the onset, that a polymer with merely a high molecular weight does not always qualify as a good sustained-release candidate.

Even for some polymers that are generally known to have the desired characteristics this may not always be true. Kassem et al. (1978) have shown that many polymers, for instance, polyethylene glycols (PEGs), polyvinyl pyrrolidone (PVP), hydroxypropyl methylcellulose (HPMC), and methylcellulose (MC), complex with drugs, such as spironolactone, *and in these cases they enhance (speed up) dissolution rates*. The general wisdom, however, is that high molecular weight polymers will aid in the formation of sustained-release dosage forms. For instance, Loftsson and Fridriksdottir (1998) have shown that PVP, CMC, and HPMC complex with γ - and β -cyclodextrin.

In fact, when the task is to enhance dissolution rate, one common practice is to cogrind the drugs with polymers, such as HPMC (Mitrevej et al., 1996) chitin, and chitosan (Koh et al., 1986a,b), microcrystalline cellulose (Nakai et al., 1978), or gelatin (Kigasawa et al., 1981). Shin et al. (1998) studied cogrinds of furosemide with crospovidone (polyplasdone, PVP). This is the opposite of sustained-releasing a

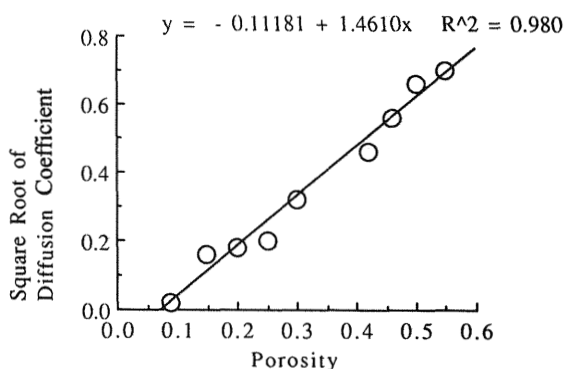


Fig. 28.5 Aspects of a rigid matrix. (Data from Towgen and Binglin, 1998.)

substance, and is mentioned here, because some of the agents used in cogrinding, when used otherwise, work as sustaining agents (e.g., HPMC).

28.7. SWELLABLE MATRICES (HYDROGELS)

Hydrogels are defined “as networks of hydrophilic polymers which can absorb a significant amount of water (> 20% of their dry weight) without dissolving or losing their structural integrity” (Vervoort et al., 1998a,b). Polymers of this type are usually cross-linked, albeit the swelling may be due to other causes, such as van der Waals forces, crystallites, hydrogen bonds, mere physical entanglement, or ionic bonds.

Most polymers will, at least, swell somewhat in water, and the most common polymer used for swellable matrices is HPMC. There are a multitude of examples of this (for example, Duddu et al., 1993).

An outline for the possibility of using HPMC in sustained-release preparations of the swellable matrix type have been described in Dow's Methocel Bulletin (1982), *Formulating Sustained Release Pharmaceutical Products with METHOCCEL*.

There is, first, a protective gel layer formed, and then two mechanisms ensue (Fig. 28.6). The pseudogel allows additional liquid to penetrate into the tablet, and this extends the gel layer a further distance into the tablet. The outer gel layer then starts to hydrate more fully and may be dissolve in the dissolution media. A steady state may then be reached, at which gel layer formation rate is balanced versus rate of erosion. However, the situation may be such that the sloughing off of gel is the controlling factor; then, the tablet simply becomes an erosion tablet. As shall be discussed further, some authors employ a power function for release (Solinis et al., 1998); that is, the amount not dissolved as a function of time will be given by

$$M/M_0 = kt^n \quad (28.37)$$

When both processes happen at similar rates, then erosion and further wetting of the tablet will continue until the all of the tablet has been penetrated and wetted, and now erosion continues until all of the tablet has sloughed off or dissolved.

The rate of diffusion is dependent on the molecular weight and the “network,” but these also affect the strength.

The first work in relation to swellable dosage forms is attributable to Lapidus and Lordi (1966, 1968), Lapidus (1967). Lapidus and Lordi prepared granulations

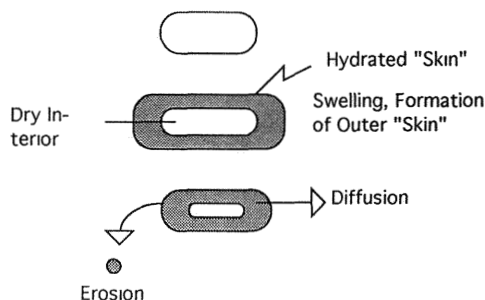


Fig. 28.6 Principle of how a hydrogel matrix functions.

by mixing the drug with the base materials and granulating with *USP* ethanol. For benzocaine, the solubility in *USP* dissolution media is very low, and the rate of release reduces to

$$Q/t^{1/2} = a[2D\varepsilon AS]^{1/2} \quad (28.38)$$

Peppas et al. (1980) have given an exact solution to the swellable matrix model using Methocel K15M, with a nominal viscosity of 15,000 cps. Many HPMC matrices (i.e., certain HPMC compositions) swell and do not disintegrate (Touitou and Donbrow, 1982)

Solomon et al. (1979a,b) used 25-kN pressure on a 500-mg KCl preparation of 1 : 1 mixture of KCl and HPMC (15000 cp). Tablets were made by direct compression, and a square-root-in-time plot was linear after 30% released and less than 70% released. Solomon et al., (1979b) in another publication reported the use of HPMC (Methocel K15M) in a study of sustained release (using KCl as a tracer) for the following reasons:

1. It may be directly compressed.
2. One obtains a gelled surface that is plane and uniform.
3. It is nonionic so that one avoids interaction with the tracer (KCl) which is ionic.
4. It exists in a large range of viscosities.

28.8. THE EROSION FUNCTION IN SWELLABLE MATRICES

It was shown in Fig. 28.6 that the manner in which HPMC matrices function involves penetration, swelling, diffusion, and *erosion*. Huber and Christenson (1966) found that the erosion function of HPMC matrices was linear in time (Fig. 28.7). However, in other systems (Bamba et al., 1979), the decrease follows a cube-root law.

The rate with which the gel sloughs off is, at times, referred to as “disintegration.” Huber et al. (1966) used HPMC 4000 cp in their work on swellable matrices

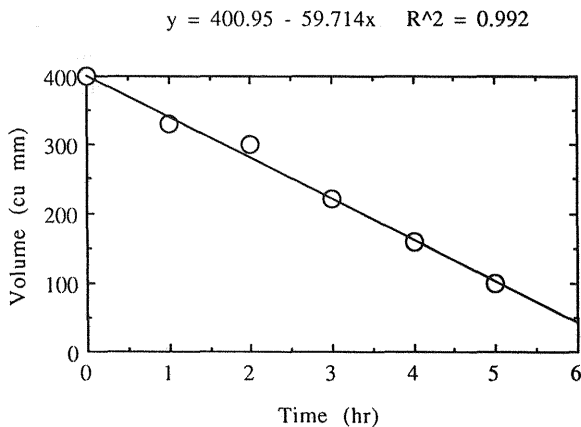


Fig. 28.7 Erosion function of HPMC matrices. (Data from Huber et al., 1966.)

and found “disintegration time” to decrease with increasing gum concentration, but noted that the behavior would differ, in quantitative terms, with different drugs and different gums. Most useful for sustained-release formulations were gums that would readily hydrate at body temperature, and they found sodium carboxymethyl cellulose (NaCMC) and HPMC to be such. For some they found constant-release rates in certain time intervals

When concentrations of HPMC become very low, especially in the poorly soluble drugs, such as naproxen, the intrusion matrix system turns into an erosion system. Chiao and Kent (1983), for instance, used 4–9% of HPMC, and when even lower percentages are used, then the dissolution may follow a cube-root law, rather than a square-root-in-time law, as exemplified by the figures in Table 28.1.

The first two columns in Table 28.1 may be plotted to give the dissolution profile shown in Fig. 28.8. Note that the curve is smooth and that there is no “lag” (i.e., the dissolution appears to begin right away). The third column in the table is the square root of the time points. If the amount dissolved is plotted as a function of the square root of time (Fig. 28.9), *then a straight line does not occur*. It is noted that this cannot be explained away by the existence of a lag time, because the trace in Fig. 28.8 exhibits no lag time.

It often happens that plots of this type are treated by the linear portion being extrapolated to zero percent release (in this case giving $t^{1/2} = 1$; i.e., $t = 1$), and it is then concluded that there is a lag time. Lag times should be extracted only from linear plots.

The fourth column in the 28.1 is the fraction not dissolved. This is obtained from subtracting the percentage dissolved from 100.00 and dividing this number by 100.00. The last column represents the cube root of the figures in the fourth column. If these figures (the cube roots of the fraction of drug not dissolved) are plotted as a function of time, then a neat straight-line occurs (Fig. 28.10).

Table 28.1 Dissolution Figures of a Moderately Soluble, High-Dosage Drug, Using 3.7% HPMC as a Granulating Agent

Time (h) released	% released	Square-root- of-time	Fraction not released	Cube-root of fraction not released
0.0	0.0	0.0	1.0	1.0
1.0	8.0	1.0	0.920	0.973
2.0	15.0	1.414	0.850	0.948
4.0	26.0	2.0	0.740	0.905
6.0	36.0	2.449	0.640	0.863
8.0	45.0	2.828	0.550	0.821
10.0	52.0	3.162	0.480	0.785
12.0	60.0	3.464	0.400	0.739
14.0	67.0	3.742	0.330	0.694
16.0	72.0	4.0	0.280	0.657
18.0	78.0	4.243	0.220	0.607

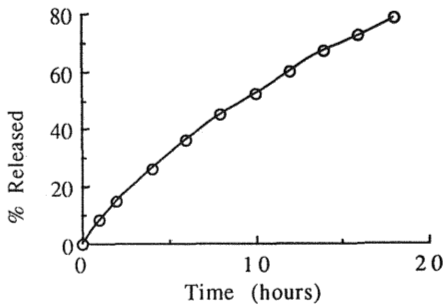


Fig. 28.8 Data from Table 28.1 where the amount of drug released as a function of time is plotted, simply, versus time (column 2 versus column 1). Note that there is no time lag, the dissolution starts immediately.

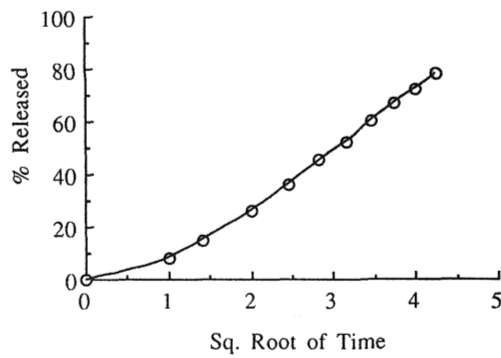


Fig. 28.9 Data from Table 28.1 plotted against square root of time.

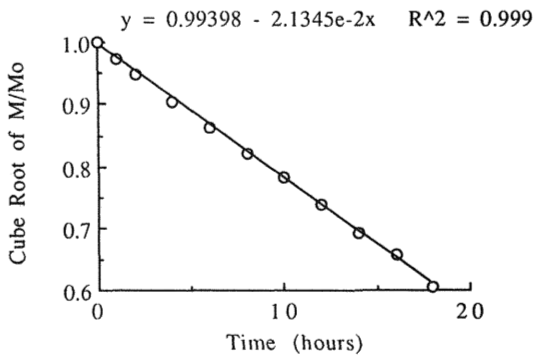


Fig. 28.10 Graph constructed from data in Table 28.1 plotted by cube root.

28.9. EFFECT OF THE AMOUNT OF POLYMER

Chiao and Kent (1983) have described a system for naproxen in which only 4–9% of HPMC is used to obtain sustained action, and the molecular weight is 80–135,000.

These amounts of polymer are low; in fact, so low that it is difficult to imagine an actual matrix of polymer, and there is a minimum amount of polymer that will form a continuous phase, given by the amount of fine drug that can be “adhered” to the solid drug. This problem was treated in an earlier chapter, and the minimum amount is a function of the surface areas, by the formula of Nyström et al. (1982) and Adolfsson et al. (1998):

$$W = 4RA_s/A_L \quad (28.39)$$

W is the smallest (critical) weight ratio of polymer to (high concentration) drug, A_s is the actual surface area of the polymer particles, and A_L is the actual surface area of the drug (which here is the component in high concentration). R is the ratio of the *specific* surface area (m^2/g) of polymer to the *specific* surface area of the drug.

W may be increased by increasing the surface area of the polymer (e.g., by micronizing it), and this is doubly effective because it increases both the value of R and that of A_s .

28.10. EFFECT OF THE MOLECULAR WEIGHT OF THE POLYMER

Christenson and Dale (1966) employed direct compression using one-third or more of HPMC. They showed that tablet hardness did not affect dissolution rates. The molecular weight of the polymer, however, was, and HPMC viscosity grades 100-, 4000- and 15,000-cp yielded $t_{1/2}$ -values of 1, 4, and 5 h.

28.11. EFFECT OF DILUENTS AND DRUG LOADING

Solomon et al. (1979a,b) used hydroxypropylmethylcellulose (Methocel K15M) in a study of sustained-release (using KCl as a tracer). It followed a square-root of time dependence with a lag time and showed the effect of the amount of HPMC on the release (half-time) of KCl.

The effect of concentration on the slope of the square-root-of-time plots is shown in Fig. 28.11. There is no consistent (or only negligible) effect on the lag time: 100 cp gives much faster release than a comparable formula with 1500 cp. The same was found by Huber and Christenson (1968), who found hardness to be of no importance. An effect of viscosity was demonstrated, and the values of $t_{1/2}$ for 100-, 4000- and 15,000-cp grades for the particular formulations were, approximately, 1, 4, and 5 h. Lapidus and Lordi (1966, 1968) and Lapidus (1967) also found that a square-root-in-time relation held true, and that it is the drug diffusivity, not the dissolution of polymer, and the water penetrability that were of importance in their system.

Because of the low solubility, the authors used the formula

$$Q/t^{1/2} = a[2D\varepsilon AS]^{1/2} = aG \quad (28.40)$$

$$y = 3.3121 - 3.2094e-2x \quad R^2 = 0.994$$

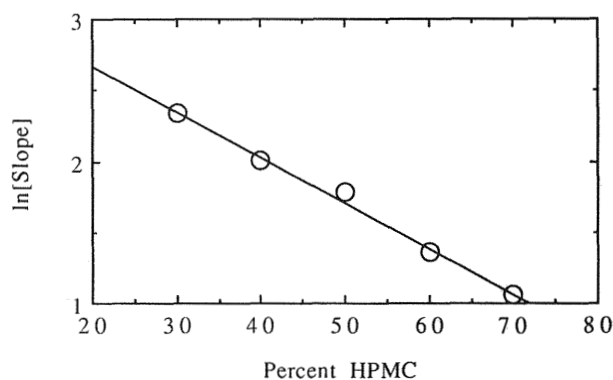


Fig. 28.11 Release rates as a function of percentage of polymer. (Data from Solomon et al., 1979a.)

for the release, where G is the square-root dissolution rate constant.

If the tablet contains soluble diluent (in a volume fraction X) and a poorly soluble drug is used, and the volume fraction of diluent is greatly larger than the other two contributors to porosity, then

$$\text{Porosity} = \varepsilon + A + X = caX \quad (28.41)$$

Hence, G should be proportional to X^2 . Lapidus and Lordi found this to be approximately true (Fig. 28.12).

28.12. MODIFIED HPMC

Attempts have been made to modify HPMC to tailor-make it to certain sustained-release requirements. Schor (1979, 1981, 1982) hydrolyzed HPMC (Methocel E-50) by exposing it to high humidity. It was mentioned that a previous patent (U. S. pat.

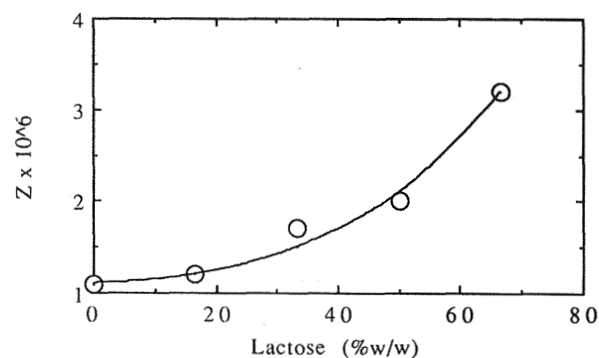


Fig. 28.12 Effect of porosity on rate of drug dissolution. (Data from Lapidus and Lordi, 1968.)

3,870,790) employed up to 25% moisture and then obtained sustained release by controlling the degree of compression. In their invention, as little as 0.5% could be present. Although the actual mechanism is not known, Schor et al. (1981) speculated that the slower-release rate arises from a decreased rate of swelling or a lower water solubility, resulting from hydrogen-bonding interaction between the carboxyl and the carbonyl groups that had been subjected to both hydrolysis and oxidation. He further improved the carrier base utilizing an HPMC grade with the following characteristics: Methocel K4M and K15M, and in one case K100, MW > 50,000, and a methoxy content of 16–24 wt%. The molecular weights were higher at the time than those used in the past and he used an amount of modified HPMC less than about one-third the weight of the sustained-release dosage form. The carrier material was always thoroughly intermixed with the medicament, which was either in a powdered or a solution form.

28.13. COMBINATION OF POLYMERS

Schor et al. (1981) reports that a 4000-cp grade of HPMC having an M_n of 93,000 is effective.

by virtue of its ability to form a soft, mucilaginous gel barrier on the surface of the tablet... [but] have found that a similar tablet prepared from 50 cps HPMC having a mean molecular weight of 23,000, e.g. Methocel E50 and Metalose 60SH50, behaves in an entirely different manner on contact with water, and forms little or no soft, mucilaginous gel barrier. When humidified and air dried in accordance with US Pat 3,870,790 and 4,226,849, the tablets proved sustained release *despite the failure to form soft mucilaginous gel*, which is obtained when the higher molecular weight HPMCs are used.

HPMC may be used in combination with ethyl cellulose (British patent, 1070492) in the absence of added water to form sustained release tablets. British patent 1,171,691 discloses a product based on the aforementioned two polymers with undefined amounts of water, the water being added by a humidification process, which is different from adding liquid water.

Lowey and Stafford (1972) and Lowey (1979) use HPMC E50 (or HPC) humidified to 5–25% moisture admixed with 20% ethyl cellulose (E4M) (e.g., for vitamin tablets).

28.14. OTHER PRESENTATION MODES AND PRINCIPLES

Some authors use the following presentation mode for dissolution of sustained release (and other) dissolution curves:

$$M/M_0 = Kt^n \quad (28.42)$$

where n would have been 0.5, had the Higuchi equation held. K is here denoted the power dissolution rate constant, and n the dissolution index.

The rate of solvent uptake has been discussed by several authors (Peppas et al., 1980; Ranga Rao et al., 1988; Vergnaud, 1993; Gao et al., 1996). Ritger and Peppas (1987a,b) use the following equation for the uptake of water in hydrogels:

$$q_t/q_\infty = kt^n \quad (28.43)$$

where q_t is the amount of solvent absorbed at times t and at infinite time.

The mean dissolution time (MDT) (Möckel and Lippold, 1993; Lippold et al., 1989) for a maximum time of N , is given by way of mean value integration of Eq. 28.2:

$$\text{MDT} = (N - 1)^{-1} K_n^{-(1/N)} N^{[N-1)/N]} \quad (28.44)$$

Sustained release by *compression coating of tablets and porosity controlling the release* has been suggested in the literature. This approach has been mentioned in Chap. 25. The compression coat contains polymers, which are semipermeable, both to the dissolving liquid and to the drug substance (Conte et al., 1983; Verhoeven et al., 1989). The release of drug from these is a function of such parameters as the amount of polymer, its surface characteristics, and its compressibility. There are limitations to the approach (e.g., the effect of the compression pressure on the physical characteristics of the polymer). Fryklof et al. (1967) employed soluble porosity modifiers to the (otherwise water-insoluble) compression coat so that, on exposure to the dissolution liquid, these would dissolve and create a porosity network (Källstrand and Ekman 1983; Zentner et al., 1985; Thombre et al., 1989). However, the pore network, in some cases, and in particular, with sorbitol, did not behave exactly as predicted. Stauffer and Aharony (1985) developed percolation theory to the problem, and this (Siegel, 1988) was used to explain the development of pore clusters and conducting channels that would span the compression coat.

Chitosan has been used in hydrogel formulae (Portero et al., 1998). Chitosan is β -(1-4)-2-amino-2-deoxy-D-glucose and is obtained by *N*-deacetylating the polysaccharide chitin. (This is a substance that is abundant in nature, being the principal component of crustaceans, insects, and shells (Muzarelli, 1977.)

28.14.1 Osmotic Pumps

The osmotic pump *principle* is demonstrated in Fig. 28.13. A core tablet containing the drug substance and an electrolyte (e.g., sodium chloride) are coated with a film that is water-permeable, but water-insoluble. A precision hole is drilled into the film.

In contact with a dissolution liquid (e.g. water), this latter will penetrate into the interior of the tablet (by diffusion and, at the onset, also through the hole).

The electrolyte and drug will dissolve and form a saturated solution of both. If the solubility of the electrolyte is S_1 mol/L, then this will create an osmotic pressure P , given by

$$P = zRTS_1 \quad (28.45)$$

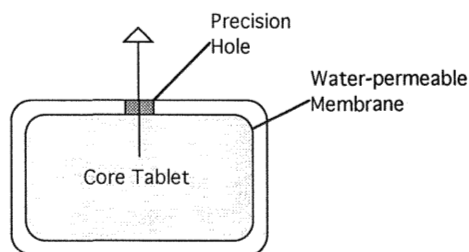


Fig. 28.13 Schematic of osmotic pump tablet.

where z is the ionic equivalence number of the electrolyte (e.g., 2 for NaCl, 3 for CaCl_2 , and so on). A pressure differential of about $P - 1$ exists between the liquid at the interior of the tablet and the bulk solution outside. The drug in solution also contributes to this, but less than the electrolyte.

Liquid, therefore, will be forced out with a velocity given by Poiseuille's law:

$$v = \pi Pr^4 / (8h\eta) = FP \quad (28.46)$$

where

$$F = \pi Pr^4 / (8\eta) \quad (28.47)$$

and where r is the radius of the hole, η is the viscosity of the liquid (in this case, the solution, saturated in electrolyte and drug substance), and h is film thickness.

As the liquid is forced out through the hole, it is replenished by (bulk) liquid diffusing into the interior and this, in turn, dissolves electrolyte and drug, so that a balance is established whereby the liquid influx equals the liquid efflux. In the steady state there is therefore,

1. Efflux of $v \text{ cm}^3/\text{s}$, containing $S \text{ g/s}$ of drug. This efflux is proportional to P .
2. Influx of $v \text{ cm}^3/\text{s}$ of dissolution medium.
3. Dissolution of vS (or vC , where $C < S$ is a steady-state concentration of drug in the efflux liquid).

The amount of drug leaving the tablet per second is then vS , and this is the "release rate." This is a zero-order release (i.e., the most desirable form of release).

The linearity will be lost once all the electrolyte or drug substance is exhausted.

28.15. FLOATABLE (BUOYANCY) TABLETS

One of the problems encountered in sustained release is the gastric emptying time. This differs from patient-to-patient, from fasting versus nonfasting conditions, and so on. One approach in overcoming this is to produce a tablet that will "float" in the stomach.

Sheth (1978) described a composition consisting 0–80% of a drug substance and 20–75% of either methylcellulose, hydroxypropylcellulose, HPMC, hydroxyethylcellulose, or sodium carboxymethylcellulose (or mixtures thereof). These compositions resulted in products with buoyancy and were formulated as a two-layer tablet with the composition such that it floats in gastric juice. This, supposedly, prolongs the residence time in the stomach.

The principle is that such amounts of HPMC and excipients are used and compression pressure so adjusted to correctly adjust the apparent density of the tablet.

28.16. CHOICE OF MODEL

The principles behind single-dose sustained-release products have been discussed in the foregoing. These models give rise to certain profiles, but many of the release profiles are fairly close to one another in appearance, and it is *often not possible by*

means of the shape of the dissolution curve, to deduct which of the mechanisms is at hand. Yet this is often being done. If so, then many models should be tested, and usually, statistical scrutiny will fail to show differences in the models.

Additional criteria can allow choosing one model over another. It might be different, for instance, to choose between an erosion and a diffusion model for a wax tablet. It is logical to choose the former, but because the diffusion model would be (fairly) independent of tablet size, and the rate constant for the erosion model is inversely proportional to the size, extra experiments might easily facilitate making a choice between the two.

Sood and Panchagnula (1998) investigated release profiles of diltiazem from a series of commercial sustained-release preparations and attempted to fit them to the following equations:

$$Q = k_0 t \quad (28.48)$$

$$\ln[M/M_0] = -k_1 t \quad (28.49)$$

$$Q = k_H t^{1/2} \quad (28.50)$$

$$1 - (M/M_0)^{1/3} = -k_{HC} \quad (28.51)$$

where M is amount not released at time t , M_0 is initial amount, Q is amount released at time t , k_0 is a zero-order rate constant, k_1 is a first-order rate constant, k_H is a Higuchi rate constant, and k_{HC} is a Hixson–Crowell rate constant. All of these equations have been discussed in the previous sections.

The authors found a linear relation between k_1 and k_{HC} , but aside from that there seemed to be no common thread in the profile fitting.

The authors then attempted fitting the profiles by methods suggested by Korsenmeyer et al. (1983), Peppas (1985), and Karajgi et al. (1993). The two latter suggest a general profile obtained from a spherical matrix, given by

$$1.5[1 - (1 - F)^{2/3}] - F = kt \quad (28.52)$$

where F is the fraction released at time t , and k is a rate constant. They also tested a power law (Korsenmeyer et al., 1983; Ritger and Peppas, 1987a,b) given by

$$Q/Q_\infty = k_R t^n \quad (28.53)$$

where n is a constant and Q_∞ is the amount released at infinite time. Equation (28.53) was a good fit, giving correlation coefficients between 0.95 and 0.99 but it is simply a type of curve fitting. A Weibull equation might also fit, but then, what would be learned from that?

SYMBOLS

A = concentration of drug (g/cm^3) in a matrix

a = (a) diameter of an erosion tablet; (b) slope of abbreviated Higuchi plot

a_0 = initial diameter of an erosion tablet

B = concentration (g/cm^3) of a diluent in a matrix

C = concentration

- D = (a) diffusion coefficient; (b) dimensionless diffusion coefficient (D_b/D_a)
 D_a = aqueous medium diffusion coefficient
 D_b = bulk diffusoin
 F = (a) $= \pi Pr^4/(8\eta)$, factor in volume expression for osmotic pump; (b) fraction released at time t
 h = (a) depth of a matrix in which all the drug has been dissolved; (b) thickness of film in osmotic pump tablet
 J = flux
 K = cube-root dissolution rate constant
 K_n = powder dissolution rate constant
 k = coefficient in the power function release rate equation
 k_H = rate constant in Higuchi equation^{1/2}
 k_{HC} = rate constant in Hixson-Crowel equation
 k_0 = zero-order rate constant
 k_1 = first-order rate constant
 L = depth of liquid intrusion
 M = undissolved drug
 M_0 = initial amount of drug
 MDT = mean dissolution time
 m = mass of an erosion or matrix tablet
 m_0 = initial mass of an erosion or matrix tablet
 N = number of particles in a sample
 n = exponent in the power function release rate equation
 P = osmotic pressure
 Q = (a) penetratioin equation constant; (b) amount of drug released per unit of surface area
 q = first-order penetration constant
 q_t = amount of solvent absorbed at times t
 q_i = amount of solvent absorbed at infinite time
 R = ideal gas constant
 r = (a) the average radius of pores; (b) radius of hole in osmotic pump
 S = solubility of drug (g/cm^3)
 S_1 = solubility of electrolyte
 T = absolute temperature
 t = dissolution time
 t_i = lag time
 V = volume of dissolution medium
 v = (a) velocity with which a liquid exits from osmotic pump tablet; (b) volume of an erosion tablet
 x = distance
 z = number of ions into which an electrolyte dissociates
 β = (a) erosion constant; (b) exponent correlating percolation porosities; (c) slope of the Higuchi plot
 ε = total porosity of the exhausted part of a matrix
 ε^* = percolatin threshold porosity
 ε_a = porosity accessible to intrusion
 $\varepsilon_d = \rho/A$ = porosity contributed by the dissolved drug
 ε_i = porosity from compression, before dissolution

η = viscosity of dissolution liquid

μ = coefficient in the relation between diffusion coefficients

Ω = integration constant in penetration equation

ϕ = (a) square-root in time constant; (b) exponent in the relation between diffusion coefficients

ρ_A = particle density of the drug substance in a matrix ε

ρ_B = particle density of an excipient in a matrix

τ = tortuosity

REFERENCES

- Adolfsson Å, Caramella C, Nyström C (1998). *Int J Pharm* 160:187.
- Adrover A, Giona M, Grassi M (1996). *J Membr Sci* 113:21.
- Asano M, Fukuzaki M, Yoshida M, Kumakura M, Mashimo T, Yuasa H, Imai K, Yamanaka H, Suzuki K (1989). *J Controlled Release* 9:111.
- Bamba M, Puisieux F, Marty J-P, Carstensen JT (1979). *Int J Pharm* 3:87.
- Caraballo I, Milán M, Rabasco AM (1996). *Int J Pharm* 13:387.
- Carstensen JT (1981). *Solid Pharmaceuticals: Mechanical Properties and Rate Phenomena*. Academic Press, New York, p 220.
- Carstensen JT, Valentine W (1966). Belgian Patent 623,704.
- Christensen GL, Dale LB (1966). U. S. patent 3,065,143.
- Conte U, Columbo P, Caramella C, La Manna A (1983). *Press-Coated Systems for Drug Release Control*. Pleunum, New York.
- Couvreur P (1975). Dissertation, Docteur Sciences Pharmaceutiques. University Catholique de Louvain, Belgium, p 87.
- Domb C (1983). In: Deutscher G, Zallen R, Adler J, eds. *Percolation Structures and Processes*. American Institute of Physics, New York, pp 17–40.
- Dow Handbook on Methocel Cellulose Ether Products [Table headed Viscosities of Methylcellulose of Various Molecular Weights].
- Dow Information Sheet (1982). METHOCCEL, No 192-886-682. British patent 1070492.
- Duddu SP, Vakilynejad M, Jamali F, Grant DJW (1993). *Pharm Res* 10:1648.
- Fernández-Hervás MJ, Vela MT, del Cerro J (1995). *Int J Pharm* 113:39.
- Fernández-Hervás MJ, Holgado MA, Fini A, Fell JT (1998). *Int J Pharm* 163:23.
- Fessi H, Marty JP, Puisieux F, Carstensen JT (1982). *J Pharm Sci* 71:749.
- Ford JL, Rubenstein MH, Hogan JE (1985a). *Int J Pharm* 23:327.
- Ford JL, Rubenstein MH, Hogan JE (1985b). *Int J Pharm* 23:339.
- Ford JL, Rubenstein MH, Hogan JE (1985c). *J Pharm Pharmacol* 37:33.
- Ford JL, Rubenstein MH, McCaul F, Hogan JE, Edgar PJ (1987). *Int J Pharm* 40:223.
- Fryklof LE, Sandell E, Ostholm GIV (1967). Medicinal tablet and a method for its preparation. U. S. patent 3,317,394.
- Gao P, Skoug JW, Nixon PR, Ju TR, Stemm NL, Sung KC (1996). *J Pharm Sci* 12:732.
- Higuchi T (1963). *J Pharm Sci* 52:1145.
- Hsiao CH, Kent JS (1983). Canadian patent 1 204 1671.
- Hsiao CH, Kent J (1993). Canadian patent 1 204 671.
- Huber HE, Dale LB, Christenson GL (1966). *J Pharm Sci* 55:974.
- Huber HE, Christenson GL (1968). *J Pharm Sci* 57:164.
- Källstrand G, Ekman B (1983). *J Pharm Sci* 72:772.
- Karajgi J, Jain NK, Vyas SP (1993). *J Drug Targ* 1:1997.
- Kassem AA, Fouli AM, Said S, Shehata E (1978). *Bull Fac Pharm Cairo Univ*.
- Kigasawa K, Maruyama K, Tanaka M, Watabe K, Kooyama O (1981). *Yakugaku Zasshi* 101:733.

- Koh IB, Shin SC, Lee YB (1986a). *Arch Pharm Res* 9:55.
- Koh IB, Shin SC, Lee YB (1986b). *J Korean Pharm Sci* 16:36.
- Konrad R, Christ A, Zessin G, Cobet U (1998). *Int J Pharm* 163:123.
- Korsenmeyer RW, Gurny R, Doelker EM, Buri P, Peppas NA (1983). *Int J Pharm* 15:25.
- Lapidus H (1967). Drug release from compressed hydrophilic matrices. University Microfilms International, Rutgers University, NJ.
- Lapidus H, Lordi NG (1966). *J Pharm Sci* 55:840.
- Lapidus H, Lordi NG (1968). *J Pharm Sci* 57:1292.
- Leuenberger H, Rohera BD, Haas C (1987). *Int J Pharm* 38:109.
- Leuenberger H, Bonny JD, Kolb M (1995). *Int J Pharm* 115:217.
- Lippold H, Sutter K, Lippold BC (1989). *Int J Pharm* 54:15.
- Loftsson T, Fridriksdottir H (1998). *Int J Pharm* 163:115.
- Lowey H (1979). U. S. patent 4,259,314.
- Lowey H, Stafford H (1972). U. S. patent 3,870,790.
- Milán M, Caraballo I, Rabasco AM (1998). *Pharm Res* 15:216.
- Mitrevej A, Sinchaipanid N, Junyaprasert V, Warintournuwat L (1996). *Drug Dev Ind Pharm* 22:1237.
- Möckel JE, Lippold BC (1993). *Pharmacol Res* 90:1066.
- Muzarelli RAA (1997). Chitin. Pergamon, Oxford.
- Nakai Y, Nakajima K, Yamamoto K, Terada K, Konno T (1978). *Chem Pharm Bull* 26:3419.
- Nogami H, Nagai T, Uchida H (1966). *Chem Pharm Bull* 14:152.
- Nyström C, Mazur J, Sjögren J (1982). *Int J Pharm* 10:209.
- Peppas NA (1985). *Pharm Acta Helv* 60:110.
- Peppas NA, Gurny R, Dolker E, Buri P (1980). *J Membr Sci* 7:241.
- Ranga Rao KV, Padmalatha Devi K (1988). *Int J Pharm* 48:1.
- Ritger PL, Peppas NA (1987a). *J Controlled Release* 5:23.
- Ritger PL, Peppas NA (1987b). *J Controlled Release* 5:37.
- Schor JM (1979). U. S. patent 4,226,849.
- Schor JM (1981). U. S. patent 4,357,469.
- Schor JM (1982). U. S. patent 4,389,393.
- Schor JM, Nigalaye A, Gaylord NG (1981). U. S. patent 4,369,172.
- Sheth PR (1978). U. S. patent 4,140,755.
- Shin S-C, Oh I-J, Lee Y-B, Choi H-K, Choi J-S (1998). *Int J Pharm* 175:17.
- Shivanand P, Sprockel OL (1998). *Int J Pharm* 167:83.
- Siegel RA (1986). *J Membr Sci* 26:251.
- Siegel RA (1988). In: Rosoff M, ed. *Controlled Release of Drugs*. VCH, New York.
- Solinis MA, Lugara S, Calvo B, Hernández RM, Gascón AR, Pedraz JL (1998). *Int J Pharm* 161:37.
- Solomon JL, Doelker E, Buri P (1979a). *Pharm Acta Helv* 54:82.
- Solomon JL, Doelker E, Buri P (1979b). *Pharm Ind* 41:799.
- Sood A, Panchagnula R (1998). *Int J Pharm* 175:95.
- Stauffer D, Aharony A (1985). *Introduction to Percolation Theory*. Taylor & Francis, London.
- Talukar MM, Van den Mooter G, Augustijns P, Tjandra-Maga T, Verbeke N, Kinget R (1998). *Int J Pharm* 169:105.
- Thombre AG, Zentner GM, Himmelstein KJ (1989). *J Membr Sci* 40:279.
- Touitou E, Donbrow M (1982). *Int J Pharm* 11:355.
- Towgen X, Binglin H (1998). *Int J Pharm* 170:139.
- Van Loo J, Coussement P, De Leenheer L, Hoebregs H, Mits G (1995). *Crit Rev Food Sci Nutr* 36:525.
- Vergnaud JM (1993). *Int J Pharm* 90:89.

- Verhoeven J, Schutte SC, Peschier LJC, Danhof M, Junginger HE (1989). *J Controlled Release* 10:205.
- Vervoort L, Van den Mooter G, Augustijns P, Kinget R (1998a). *Int J Pharm* 172:127.
- Vervoort L, Rombaut P, Van den Mooter G, Augustijns P, Kinget R (1998b). *Int J Pharm* 172:137.
- Washburn EH (1921). *Phys Rev* 17:273.
- Zentner GM, Rork GS, Himmelstein KJ (1985). *J Controlled Release* 2:217.

This Page Intentionally Left Blank

Sustained-Release by Microencapsulation

29.1. Sized Particles	494
29.2. Application of Films	495
29.3. Coated Particles	496
29.4. Coated Nonpareils	498
29.5. Multiple Osmotic Pump Principle	499
29.6. Film–Thickness-Coated Granules	501
29.7. Discontinuous Films	503
29.8. Continuous Films	503
29.9. Use of a Mixed Film and Multiple Films	503
29.10. Tableted Microcapsules	504
29.11. Ethyl Cellulose Films	504
29.12. Nonsink Conditions	505
29.13. Other Films	507
Symbols	508
References	509
Recommended Reading	510

Attaining sustained release through particle size manipulation and coating are the subjects of the following. The former will be treated first. The aim of the chapter is to cover *principles and theory* of products sustained by sizing and by coating. It is *not* the purpose to cover details about processes, examples, and raw material selection, and for that purpose the reader is referred to the *Recommended Reading* at the end of

the chapters. Some coverage of processes and raw materials will be given to the extent needed for covering the principles and theory.

29.1. SIZED PARTICLES

It is known from previous chapters that particles will (often) dissolve by a Hixson-Crowell cube-root law:

$$1 - \{M/M_0\}^{1/3} = Kt \quad (29.1)$$

where K , for a sphere is given by

$$K = 2kS/(r\rho) = Q/r \quad (29.2)$$

which in Cartesian notation takes the form

$$M = M_0\{1 - (Q/r)\}^3 t^3 \quad (29.3)$$

It is easy to visualize that Eq. (29.2) could allow calculation of some size r , at which the value of K and hence, the dissolution profile given by Eq. (29.3) would be “sustained” to a set of specification one might require for sustained in vivo and in vitro release patterns.

The problem is that the values of r could be outside the pharmaceutically acceptable range, which is largely from submicron range to about $500\ \mu\text{m}$. Nevertheless, there are substances for which this is a practical solution (e.g., nitrofurantoin, and to some degree, naproxen). The release patterns can be adjusted a bit by mixing the best fraction with small amounts of other fractions to “adjust” the profile.

The following notation will be used in the immediate following:

M = mass not dissolved

M_0 = initial mass before dissolution

K = cube-root dissolution rate constant

t = time

ρ = density

k = intrinsic dissolution rate constant (cm/s)

S = solubility (g/cm^3)

r = radius of a spherical particle

$Q = 2kS/r$

t = time

As an example, assume that Q is 1.0 and $r = 100\ \mu\text{m}$. In that case the results of fraction released are those shown in Fig. 29.1 and column 2 in Table 29.1. The second and third column show release rates for particles of sizes 75 and $50\ \mu\text{m}$.

Suppose one desired to obtain 30–40% released in the first hour, 70–80% in the third hour, and over 80% after 6 h. It is seen that the plain mesh cuts do not meet the requirement for the first and third hour, whereas mixes do. It is often possible, by manipulation and mixing of mesh cuts to obtain a desired release profile.

Naproxen is another substance that gives a (almost) 12-h in vivo release when simply administered as a particle. Small amounts of HPMC will prolong this to 24 h.

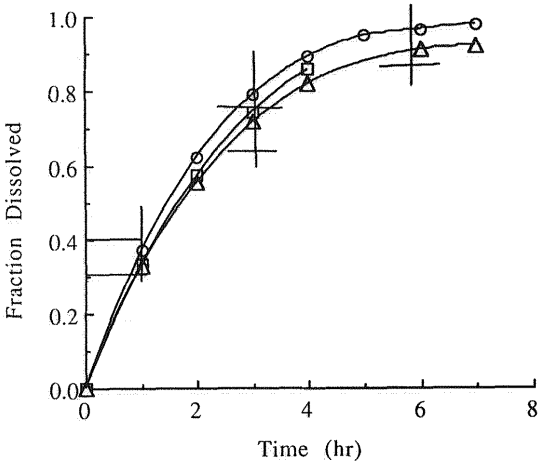


Fig. 29.1 Ratios of 100 to 75 to 50 μm : circles 1:1:1, squares 3:2:1, triangles 1:4:6.

29.2. APPLICATION OF FILMS

Particle size manipulation is not a common way of producing sustained action. The most common method is by coating the particulate solid with a film, which is most often water-insoluble, but water-permeable.

Films may be applied in one of four ways:

- 1. Pan coating
- 2. Fluid bed coating
- 3. Coprecipitation (coascervation)
- 4. Evaporation

In method (1), the film solution is sprayed onto tumbling beads, until a certain degree of wetness, and so that the beads do not grow together; the spray is halted intermittently, and drying by hot air is carried out. This is continued until “the desired film thickness” is acquired. *This is not one continuous film that is produced,*

Table 29.1 Release Rates According to Eq. (29.3) with $Q = 1.0$ and Different Size Particles

Time	100 μm	75 μm	50 μm	Ratio 1:1:1	Ratio 3:2:1	Ratio 1:4:6
0	0	0	0	0	0	0.329
1	0.271	0.350	0.488	0.37	0.334	0.557
2	0.488	0.606	0.784	0.626	0.575	0.717
3	0.657	0.896	0.936	0.790	0.745	0.818
4	0.784	0.96fa3	0.992	0.891	0.856	0.908
5	0.875	0.992	1	0.946		0.919
6	0.936	1	1	0.964		
7	0.973	1	1	0.976		

but rather a series of films of the same composition. The films, if the coating is carried out correctly, anchor together well, but it is still, principally, a series of films, and the presence of intrusion liquid and the subsequent pressure buildup may make the adhesion planes into pores, so that the principle, rather than a continuous film principle, becomes a coat-sieve principle.

The same may be argued for process (2), although only partly. In a fluid bed (e.g., in a Wurster apparatus), the seeds or beads pass through a zone of mist application, and then up in a chamber and down again, just to be returned through the mist zone. If the seeds or beads are completely dry when they reenter the spray zone, then the situation is the same as in the coating pan application, but if they are still somewhat moist, then the anchor between "layers" is actually continuous, and the film becomes continuous.

In method (3) which will be discussed in more detail shortly, the film is actually deposited by precipitation on the seeds or beads, and such films are, or can be, completely continuous.

Method (4) is, strictly speaking, not a film, but rather, a matrix. Each *individual* drug particle is coated, but not with *one particular film*, and there is (or can be) drug particles in the surface of the film. The drug release is akin to that of matrix tablets covered in Chap. 28.

29.3. COATED PARTICLES

There are films that are water-insoluble (e.g., certain grades of ethyl cellulose), or only slowly soluble in water (e.g., certain grades of HPMC or HPC), so that when a pellet (granule, bead) consisting of drug, or of drug and some excipient, is coated with the film-former, then a situation in Fig. 29.2 will arise. The particle will be denoted a *coated bead or microsphere* in the following. (Many types of nomenclature exists, microcapsule being one.)

At first [see situation (a) to (b) in Fig. 29.2], liquid will penetrate the coated bead. The intrusion liquid will dissolve some of the drug and excipient to form a saturated solution. There may be some expansion of both the interior of the coated

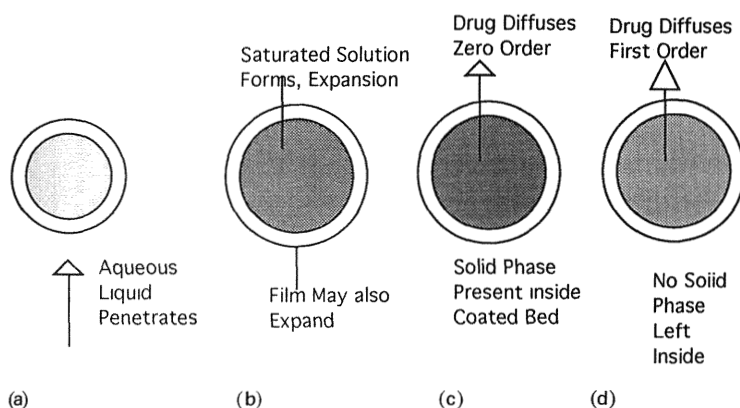


Fig. 29.2 Schematic of a bed coated with a water-insoluble, water-permeable film.

particle and the film itself. This period is denoted the *lag time* in the following, and is designated by the symbol t_l . This is, obviously, a non-steady-state period.

Once a saturated solution is formed in the interior, the concentration gradient will be constant, S/h , where S is saturation, and h is the thickness of the film at stages (b), (c), and (d). (This may be somewhat larger than the film thickness of the dry-coated bead.)

At one point, $t = t^*$, the last particle of drug will have dissolved, and from this point on, the concentration gradient is, under sink conditions at the exterior, proportional to the concentration C , at the interior of the bead, and the rate will be given by

$$dM/dt = -ADC/h \quad (29.4)$$

where M is drug mass not dissolved at time t , D is diffusion coefficient, and A is surface area. If the total volume of the interior of all the beads is denoted V , then

$$C = M/V \quad (29.5)$$

so

$$dM/dt = -(AD/Vh)M \quad (29.6)$$

or, integrated:

$$\ln[M/M_0] = -\{(AD/Vh)\}t \quad (29.7)$$

This will be treated further in Sec. 29.12. If the process is approximated by the three zones (a) $\rightarrow$ (b), lasting t_l hours, (c) lasting $t^* - t_l$ hours, and (c)–(d) after t^* , then a schematic graph OAB will result (Fig. 29.3). However, transitions in (a)–(b) involves some release, and both that and the transition to post-steady-state will be gradual.

The following considerations assume that the film is *continuous*. This will be discussed further at a later point in the chapter.

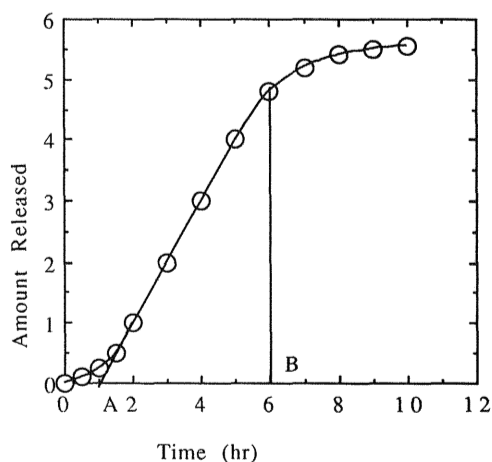


Fig. 29.3 Idealized release profile of a situation such as shown in Fig. 29.2. g_l occurs at A (i.e., at 1 h, and t^* , the transition to first order, post-steady-state, occurs at B (6 h).

29.4. COATED NONPAREILS

The type of interior of a coated bead can be either a nonpareil seed (a sized sugar crystal, mostly 40 mesh), an extruded pellet (Rork and Haslam, 1994), or simply a granule from a wet granulation. In the simplest case it may be simply a drug particle.

Nonpareil seeds are the original type of continuous sustained-release product, patented in 1950 by Smith Kline & French. In it, nonpareil seeds (sized sugar; e.g., monodisperse at 40 mesh), are coated with (most often a syrup suspension of) the drug, and the dry, now rounded beads are coated with an insoluble, semipermeable coating.

The coating may be either one semipermeable coat, or may be a coat made from an insoluble, semipermeable material mixed with a water-soluble material. The former will be discussed first.

The mechanism in the former is the same as discussed in Sec. 29.2, in that dissolution medium penetrates into the interior of the coated bead, dissolves the sucrose and the drug to form a saturated solution of both. Saturated sugar increases the osmotic pressure (but not nearly to the extent of electrolytes), and the situation is primarily that a saturated solution of the drug is inside the coat, and diffuses out into a bulk solution under semisink conditions. The point at t^* is where all the drug is dissolved, but if all of the sugar is dissolved at an earlier point, the content of dissolved sugar will decrease (by diffusion), and the osmotic pressure will decrease. This may give rise to a decrease in rate, but the magnitude of this is less significant than the point where the drug has just all dissolved.

The following nomenclature will be used in the following:

N = number of coated beads

$S(\text{g}/\text{cm}^3)$ = solubility of drug

a (cm) = inside diameter of bead [at stage (b)]

h = thickness of film

q = grams of filler (e.g., nonpareils) per coated bead

f = grams of fill of the coated bead that is drug

w = weight of fill ($= q + f$)

W = encapsulated dry weight [$= N(q + f)$]

V = volume of the interior of all the dry, coated beads

Q = total dose of drug dosage form ($= fN$)

ρ = weighted density average of the dry solids in the coated beads

With use of the foregoing nomenclature, the following holds for the (total) steady-state release rate of drug substance:

$$dQ/dt = N(\pi a^2)DS/h \quad (29.8)$$

The total weight of dry interior of the N coated beads is

$$W = N\rho(\pi a^3)/6 \quad (29.9)$$

so that

$$N = 6W/(\rho\pi a^3) \quad (29.10)$$

Equation (29.10) inserted in Eq. (29.8) then gives

$$dQ/dt = (\pi a^2)DS6W/(h\rho\pi a^3) = 6SDW/(h\rho a) \quad (29.11)$$

At a given fill weight and dose, in the steady-state region (A to B in Fig. 29.3) the release will, again, be zero-order, with a rate of $6SDW/(h\rho a)$, i.e., the rate will be slower under the following conditions.

1. The larger a is (or, equivalently, the smaller N is)
2. The larger h is
3. The smaller D is
4. The smaller the solubility is

If, on the other hand, the w , the fill weight, is kept constant, but the drug concentration, $f/(f+q)$ is increased, then the number of particles N , will decrease, and by Eq. (29.8) the overall release rate, dQ/dt , will decrease. However, the value of t^* , the length of steady-state, will increase.

If the film thickness increases, release rates go down, and the lag time t_l , increases. It is, therefore, as in Table 29.1 with sized particles, possible to blend fractions of coated beads of different film thickness, to obtain a final release curve that is a linear combination of the individual release curves, weighted according to their fraction.

There is a danger in this, because blending of particles that do not percolate can be difficult, if not impossible. Also, *if fill weight is adjusted with placebos, one should use placebos of approximately the same size as the coated bead*. In the nonpareils there has been past practices in which the blank nonpareils were used as fillers, resulting in devastating content uniformity problems.

Desired release profiles, therefore, may be obtained by manipulation of these quantities when adequate polymers are used. Because the dry weight is given by $W = N(q+f)$, a reduction in q will make W smaller.

29.5. MULTIPLE OSMOTIC PUMP PRINCIPLE

If an insoluble film-former is mixed with a minor component that is soluble or leachable, then this component, when the film is exposed to aqueous liquid, will disappear from the film, leaving "holes," so that the unit will act in a manner of an osmotic pump. The film must be a two-phase system to work in this manner (i.e., the minor component must be insoluble in the major film-former, or the film must be sufficiently weak that the osmotic pressure formed on liquid intrusion will make the film yield and form channels through which the dissolved drug can escape).

The most common coating is plasticized ethyl cellulose, or ethyl cellulose containing a water-soluble polymer (such as PEG). In the former case the process that takes place when the microcapsule comes in contact with dissolution liquid (e.g., water) is

1. (a) Water penetrates and swells the coating, and (b) water dissolves the soluble plasticizer.
2. Water penetrates into the interior of the sphere, fills it, and becomes saturated with drug (and or excipient, e.g., sugar, in a nonpareil seed), and this increases the osmotic pressure P .
3. Solution, saturated in drug substance, is forced out through the holes formed in the coating.

4. This continues until all solid drug in the interior of the microcapsule has been dissolved.
5. A terminal phase results where the concentration, C inside the sphere, decreases until it equals the concentration in the bulk liquid.

If the weight of the film is H , and a fraction of it is such a pore former α , then the following holds. Coated beads are made by conventional means and the "weight" of the holes is,

$$\text{Weight of pore former} = \alpha H \quad (29.12)$$

There are n holes of diameter δ , and there are several ways of *visualizing* how they can be arranged in the film. The volume λ , of the n particles is given by

$$\text{Volume of hole material} = hn\pi\delta^2/4 \quad (29.13)$$

The density of the hole material is ρ' , so the weight of the holes is

$$\text{Weight of holes} = hn\rho'\pi\delta^2/4 = \alpha H \quad (29.14)$$

so that the number of holes n , may be expressed as

$$n = 4\alpha H/(\rho'\pi\delta^2) = E/\delta^2 \quad (29.15)$$

where

$$E = 4\alpha H/(\rho'\pi h) \quad (29.16)$$

E is constant for a given application.

The bead works as an osmotic pump (i.e., the rate v , of volume release of saturated liquid in the steady-state zone *per hole* will be

$$v_1 = \pi P\delta^4/\eta h \quad (29.17)$$

where η is viscosity.

The total rate v is the rate per hole times the number of holes (i.e., using the expression for n derived earlier).

$$v = nv_1 = \{4\alpha H/(h\rho'\pi\delta^2)\}\{\pi P\delta^4/\eta h\} = GP\delta^2/\eta h^2 \quad (29.18)$$

where

$$G = 4\alpha H/(\rho') \quad (29.19)$$

is a constant for a given application.

The total rate of release (dM/dt) is the rate of volume release v , multiplied by the concentration of drug, which is S during the steady-state period, so that

$$dM/dt = ESP\delta^2/\eta h = 4\alpha HSP\delta^2/(\eta h^2\rho_H) \quad (29.20)$$

It is seen that the release rate in the linear, steady-state portion is

1. Proportional to the solubility of the drug
2. Proportional to the diameter of pores squared
3. Inversely proportional to the *viscosity* of the solution saturated in filler and drug
4. Inversely proportional to the film thickness squared

The diameter of the pores squared is a process-dependent term, so that process reproducibility is of great importance. It is an approximate picture anyway, because the holes are not going to be cylinders; they may be tortuous, but the overall effect is well described by Eq. (29.20).

Often overlooked is that the solubility of the "filler" contributes in two ways: first, in increasing the osmotic pressure P ; second, in increasing the viscosity.

The pore material is selected as a material that is *insoluble* in the polymer. Plasticizers are usually not good pore materials because they are soluble in the polymer. They reduce the glass transition temperature by being soluble. Hole material is best insoluble in the polymer, and in this case a thermogram (or better yet a torsion braid balance profile) shows two transition temperatures, one for the polymer, one for the pore former.

Ethyl cellulose and HPC, of certain grades are mutually soluble, and when using EC in such applications, the pore-forming model should not hold. Polyethylene glycol of certain molecular weights, on the other hand, seems fairly insoluble in high molecular weight ethyl celluloses, and would be good pore formers. Again, the *percolation threshold* must be exceeded.

These concepts lead to the following point of view. In coating with *continuous films*, it should be recalled, that a film deposited by fluid-bed-spraying method, is not necessarily a continuous film, but rather, could be a series of films, well anchored together. However, in contact with water, when an initial amount has penetrated by diffusion, the osmotic pressure developed by dissolution of filler and drug substance causes a stress of the film, and channels may develop in the adhesion planes of the various layers of which the "continuous" film is made up.

This may, actually, be the method of release of many continuous-film products.

29.6. FILM-THICKNESS-COATED GRANULES

The effect of film thickness h has been mentioned on several occasions in the foregoing. It is obvious that the amount of film H that is applied relates to the film thickness of a monodisperse population of beads of diameter a , by the relation

$$H = N\rho'h\pi a^2 \quad (29.21)$$

where ρ' is the density of the film. The weight W of the beads is given by Eq. (29.9) $W = N\rho(\pi a^3)/6$, repeated here for convenience, where ρ is the density of the solid. Inserting Eq. (29.10) into Eq. (29.21) then gives:

$$H = 6W\rho'h\pi a^2/[\rho(\pi a^3)] = 6W\rho'h/(\rho a) \quad (29.22)$$

For a desired film thickness h and bead particle size a the ratio of weights of film-former to dry seeds or beads is, therefore,

$$H/W = 6\rho'h/(\rho a) \quad (29.23)$$

For monodisperse populations, the seeds or beads are simply loaded into the appropriate apparatus (pan, fluid bed dryer, reaction vessel), and the film thickness will be (fairly) uniform, and can be calculated from Eq. (29.21).

In some applications, granulations are made and sized to a certain particle size *range* (e.g., the smallest diameter is $a_{\min}$ and the largest $a_{\max}$; Fig. 29.4).

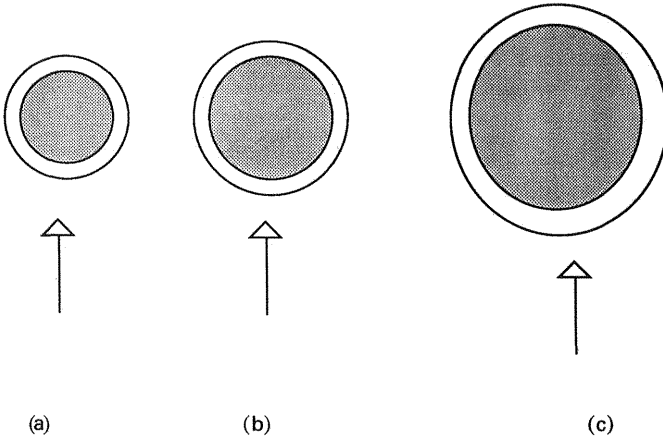


Fig. 29.4 Principle of thickness control by way of particle size distributions.

Because the seeds or beads are in a stream of coating spray, the amount adhering to them would either be a function of the actual surface area, so that the amount applied to each fraction would differ.

The amount of film, H applied to a particle is assumed proportional to the surface area of the particle. The amount H_i applied to the i th fraction of particle size a_i would, therefore, be

$$H_i = \beta n_i \pi a_i^2 \quad (29.24)$$

where β is a proportionality constant and n_i is the number of particles in that fraction. If the i th fraction acquires a film thickness of h_i then

$$H_i = n_i h_i \pi a_i^2 \rho' \quad (29.25)$$

The film thickness, h_i , of the i th fraction would be given by [Eq. (28.25) and (28.24)]:

$$H_i = h_i (n_i \pi a_i^2 \rho') = \beta n_i \pi a_i^2 \quad (29.26)$$

from which:

$$h_i = \beta / \rho' \quad (29.27)$$

The release of material, q_i , from the i th fraction is given by Fick's law:

$$dq_i/dt = DS n_i \pi a_i^2 / h_i = n_i DS \pi a_i^2 \rho / \beta \quad (29.28)$$

so that the total release rate is given by

$$dQ/dt = \Sigma n_i DS \pi a_i^2 \rho / \beta = \{DS \rho^N / \beta\} \Sigma f_i a_i \quad (29.29)$$

where

$$f_i = n_i / N \quad (29.30)$$

is the number fraction of particles in the i th interval.

When N is large, this may be written

$$dQ/dt = \{D^S \rho^N / \beta\} \int_{a(\min)}^{a(\max)} f(a) a^2 da \quad (29.31)$$

where $f(a)$ is the particle size number distribution. It is noted that the integral is the second-moment of the distribution function, and that this, μ_2 is equal to the variance of the distribution (Bennett and Franklin, 1961).

29.7. DISCONTINUOUS FILMS

Pan coating was used, almost exclusively, until the development (in the 1960s) of fluid bed towers (Wurster columns) that allowed the spraying of a coating solution onto a small particle. Both pan coating and spray coating of fluidized bed result in films that are several film layers deposited, one on top of the other. Depending on the "wetness" of the first film at the time the second is deposited, and the n th film at the time the $(n + 1)$ st is deposited, the film may be more or less continuous. The fact remains that the film will have weak planes, and the increased osmotic pressure on liquid intrusion during use, may or will make it act like a multiple osmotic pump.

The original sustained-release product patented by Smith Kline & French in 1950, used shellac as a sustaining agent and employed pan coating. Because of the tendency of shellac to polymerize on storage, it is, by now, largely abandoned in new formulation. Other compounds (e.g., waxes) have been used on occasion, but mostly in combination with other compounds.

Powell (1971) adds wax to an ethyl cellulose film in such a manner that it becomes part of the polymeric walls. The ethoxyl content of the ethyl cellulose used was 48–49.5% and it had a viscosity of 90–10 cp in 80:20 toluene/ethanol at 25°C. When large amounts (> 20%) of wax are used, then "excess wax . . . remain[s] undissolved and start covering walls of the coated beadlet. Such coatings alter the release characteristics."

Cellulosic derivatives (EC, HPC, HPMC) are the polymers usually considered in new-product formulation nowadays, and these will be dealt with, in the following.

29.8. CONTINUOUS FILMS

Continuous films (such as depicted in Fig. 29.2) are, in general, produced by coprecipitation. A wax coating, deposited by melting and cooling, will also be continuous, but waxes are rarely used as *films*.

The continuous films of substituted cellulose-type polymers are often produced by coprecipitation. One way to obtain a continuous "wall" is by temperature effects. A solvent dissolves the polymer at higher temperature, the temperature is dropped, and the polymer precipitates out on the suspended active substance.

29.9. USE OF A MIXED FILM AND MULTIPLE FILMS

The original concepts are of the type shown in Fig. 28.2. However, the multiple osmotic pump principle was developed soon thereafter by use of mixed coats. It is often uncertain, whether these mixtures provide the mechanical equivalent of an osmotic pump (by leaching out the minor water-soluble ingredient), or whether

this latter is present as a plasticizer (i.e., forms a solution with the major ingredient). These two situations may be distinguished by means of glass transition temperature determination. The lowering of the main peak of the major component without the appearance of a peak for the minor component will indicate solubility; hence, plasticity. But, if the film is continuous, then the release of drug would occur by erosion and diffusion, whereas if the film is discontinuous, or if the minor component is insoluble in the film-former, then leaching may occur, and the multiple osmotic principle may prevail.

Hsiao (1985) teaches the use of a mixed coat of ethyl cellulose and hydroxypropylcellulose and the use of coprecipitation in its manufacture. The author uses type 10 (10 cp) ethyl cellulose, and Klucel LF, in a ratio of 7 parts to 3 parts. The patent describes the application of a coat of quinidine unto nonpareil seeds. "Each pellet has a coating of quinidine over nonpareil seed. The quinidine coated nonpareils are then coated with a mixture of... ethylcellulose to... hydroxypropylcellulose. The inventor states: "the more water-soluble hydroxypropylcellulose in the outer coating provides 'channels' for the water to enter and, over a period of time, leach out the quinidine disposed on the nonpareil seed." In claim 1 they state: "pellets... of a coating of quinidine over a nonpareil seed, the thus quinidine coated nonpareils are coated thereon with a coating... of 9 parts ethylcellulose to a part hydroxypropylcellulose..." (i.e., advocating more than one coat in the dosage unit).

29.10. TABLETED MICROCAPSULES

Hermelin (1963) in the early 1960s implied the possibility of tableting coated beads. U. S. patent 3,115,441 (Hermelin, 1963) discloses a tableted composition comprising particles of medicament covered by several individual layers of enteric-coating material and included in a matrix of medicament and filler. Enteric activity is provided only at the surface of individual particles.

Practical solutions to direct tableting of coated beads is tied in with the development of very high molecular weight ethyl celluloses. These have exceptional strength, and their pharmaceutical use is attributed to Hsiao (1987) who makes a claim "where the plurality of pellets are compressed into a tablet." The concern of breaking coated pellets during compression, even with the very strong films provided by high molecular weight ethyl cellulose is voiced by Hsiao (1985) who states that

[T]he coated aspirin is mixed with a compression aid, such as microcrystalline cellulose.... By incorporation of a compression aid, less force is required to compress the mixture into tablets thereby minimizing disruption of the polymer film coating the aspirin crystals.

29.11. ETHYL CELLULOSE FILMS

Ethocel (EC) has been used as a membrane substance in sustained-release beads, often in combination with other polymers, such as hydroxypropyl methylcellulose (HPMC) and hydroxypropylcellulose (HPC).

Guyot and Fawaz (1998) made microspheres of nifedipine using ethyl cellulose/HPMC by means of solvent evaporation. They found that drug incorporation was less efficient in EC microsphere when the viscosity of the organic phase was

increased. On the other hand, it was enhanced by decreasing the EC/HPMC ratio or the EC/HPC ratio, and the authors concluded that the nifedipine was present as an amorphous phase. The microspheres exhibited no burst effect.

Ethyl cellulose coating to attain sustained release has been treated extensively in recent literature (Porter, 1990; Lippold et al., 1989; Yuen et al., 1997; Yang et al., 1992; Bianchini et al., 1993). The importance of some variables are demonstrated: for example, Bianchini and Vechio (1989) have demonstrated the effect of loading on release, and Rowe (1986) has shown the effect of molecular weight on the properties of the ethyl cellulose film.

Usually, plasticization of the ethyl cellulose is accomplished by either HPMC, HPC, or PEGs. Belleville et al. (1979), for instance, used HPMC as coating material with Ethocel. The ethyl cellulose may be applied as a solution in (20% methylene chloride in methanol) or in suspension form (e.g., Surelease, ethylcellulose pseudo-latex). The higher the molecular weight of the polymer, the less is necessary, and the stronger the film. When solvent is added and plasticized with HPC, a film strong enough to withstand tableting pressures may result.

Suspensions are usually added in fluid bed equipment (e.g., Uniglatt, Germany). When suspensions are employed, good linear release is obtained with the coated pellets, but not all microspheres made in this manner withstand tableting (Palmieri and Wehrli, 1997). The release patterns are shown in Fig. 29.5.

29.12. NONSINK CONDITIONS

As mentioned in Fig. 29.2, the phases (a) $\rightarrow$ (b) require a certain length of time, t_l , a lag time, to be established. The subsequent release profile was treated in the previous sections as dictated by sink conditions (i.e., the concentration in the bulk liquid surrounding the coated bead were zero). If this were not so, then the dissolution profile would be dictated by the following considerations: The dissolution medium will have a volume of $V \text{ cm}^3$. There will, originally, be a total of M_0 mg of drug substance in the coated beads. The solubility of the drug substance is $S \text{ mg/cm}^3$ and $M_0 < SV$ for complete dissolution to be possible. The surface area of the beads is $A \text{ cm}^2$ and the thickness of the coating is $h \text{ cm}$ as in past sections.

The flux through the film is, under nonsink conditions given by

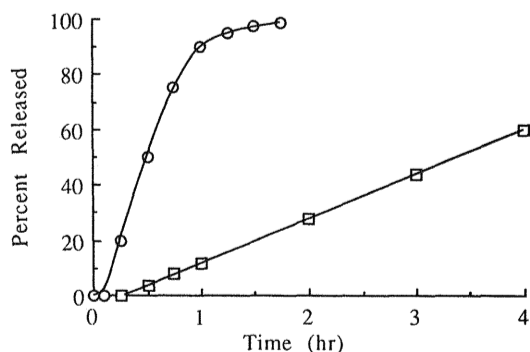


Fig. 29.5 Release patterns of coated pellets. (Data from Palmieri and Wehrli, 1997.)

$$dM/dt = -(AD/h)(S - C) \quad (29.32)$$

It is noted that C is the concentration in the dissolution medium and that it increases as a function of time. The concentration in the dissolution medium is given by

$$C = (M_0 - M)/V \quad (29.33)$$

This is inserted in the expression

$$dM/dt = -\{AD/(h)\}(S - C) \quad (29.34)$$

and results in the following:

$$\begin{aligned} dM/dt &= -[DA/(h)]\{S - [(M_0 - M)/V]\} \\ &= -\{DA/hV\}\{[SV - M_0] + M\} \\ &= -\beta\{q^* + M\} \end{aligned} \quad (29.35)$$

where

$$[DA/(Vh)] = \beta \quad (29.36)$$

and

$$(SV - M_0) = q^* \quad (29.37)$$

Integration of this yields (noting the initial condition dictated by t_i)

$$\ln\{(q^* + M)/(q^* + M_0)\} = -\beta\{t - t_i\} \quad (29.38)$$

where the initial condition, that $M = M_0$ when $t = t_i$ has been invoked.

If q is small, then the Eq. (29.38) reduces to

$$M = M_0[\exp(-\beta(t - t_i))] \quad (29.39)$$

The value of β should be inversely proportional to the thickness of the film. The amount Q of a material deposited on a sphere of diameter, d , is given by

$$Q = N\rho\pi d^2 h \quad (29.40)$$

where N is the number of particles in the sample. Hence, β should be inversely proportional to Q .

Data by Palmieri and Wehrle (1997) are shown in Fig. 29.6. The data are pellets coated with Ethocel latex suspensions (Surelease) in a fluid bed granulator. Four different amounts of ethyl cellulose were applied, and when the data are combined and plotted in reduced time coordinates by the method of Carstensen (1996), it is obvious that *all* the data are of the same general type profile.

In this case the value of q is small, and furthermore the lag time is close to zero, so that now Eq. (29.38) becomes approximately

$$M = M_0[\exp(-\beta^* t)] \quad (29.41)$$

Hence, plotting of $\ln[M/M_0]$ versus time should give a plot of slope β , and intercept zero. That this is (approximately) so is demonstrated in Fig. 29.7. The intercepts are *not* quite zero, but this is because there, indeed, is an ever so slight lag time, which has been disregarded.

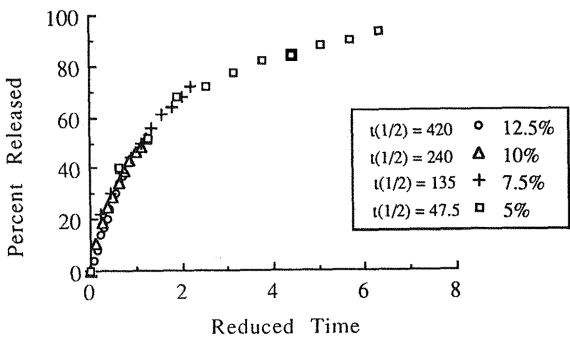


Fig. 29.6 Release patterns of pellets under nonsink conditions. (Data from Palmeri and Wehrlé, 1997.)

The slopes of the lines in Fig. 29.7 are shown in Table 29.2. They are plotted in Fig. 29.8. The inverse relation is fairly linear, but undoubtedly somewhat curved, and the slope of the linear approximation is not unity, but 0.5.

The reason for this is that, in actuality, Eq. (29.40) should read

$$Q = (N\rho\pi/6)\{(d + h)^3 - d^3\} \tag{29.42}$$

Equation (29.36) may be written $h = [DA/(V\beta^*)] = \phi/\beta$ so that

$$Q = (N\rho\pi/6)\{3d^2(\phi/\beta) + 3d(\phi/\beta)^2 + (\phi/\beta)^3\} \tag{29.43}$$

The treatment, nevertheless, lends credence to the modeling shown here.

29.13. OTHER FILMS

There are other sustained-action polymers in use, and one of these is chitosan. This has gained considerable interest in recent years as a polymer to be used in microsphere formulation (He et al., 1998,1999; Acikgoz et al., 1996; Bavin et al., 1984; Chwala et al., 1994; Conte et al., 1994; Palmieri et al., 1994; Hassan et al., 1992).

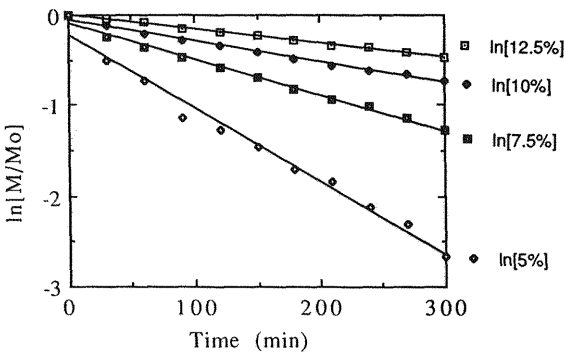


Fig. 29.7 Graph constructed from data in Fig. 6 in publication by Palmeri and Wehrlé (1997).

Table 29.2 Least-Squares Fit Data from Fig. 29.7

% Coating	Intercept	Slope $\times 10^3$	R^2
12.5	0.0013	1.5381	0.998
10	-0.051	2.344	0.989
7.5	-0.091	3.9673	0.992
5	-0.23	8.0153	0.982

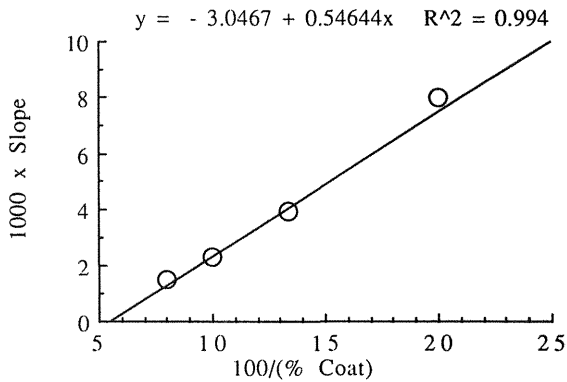


Fig. 29.8 Data from Table 29.2 plotted as slope versus the inverse of coating amount.

A host of other compounds are also being investigated and reported in current literature. For example, Santhino et al. (1999) have developed methods for making casein microparticles, which have promise for targeting of drugs.

SYMBOLS

- A = surface area
- a = inside diameter of bead
- $a_{(\max)}$ = maximum particle size of a granulation
- $a_{(\min)}$ = minimum particle size of a granulation
- C = concentration at the interior of the bead
- D = diffusion coefficient
- E = constant $(4\alpha H/(\rho'\pi)$ or $4\alpha H/(\rho')$
- H = mass (weight) of film
- H_i = film weight on the i th fraction of coated granules
- h = film thickness
- K = cube-root dissolution rate constant
- f = grams of fill of the coated bead that is drug
- k = intrinsic dissolution rate constant (cm/s)
- M = mass not dissolved
- M_0 = initial mass before dissolution

N = number of coated beads

n = number of pores (holes)

n_i = the number of particles in the i th fraction

P = osmotic pressure

Q = (a) $2kS/r$ in Hixson–Crowell equation; (b) total dose of drug dosage form ($= fN$); (c) amount released

q = grams of filler (e.g., nonpareils) per coated bead

q^* = constant in nonsink conditions

q_i = the amount released from the i th fraction

r = radius of a spherical particle

S = solubility, g/cm³

t = time

t^* = critical time at which the last particle of drug will have dissolved

V = volume of the interior of all the dry, coated beads

v = total volume of liquid released through pores

v_1 = volume of liquid released per pore

w = weight of fill ($= q + f$)

W = encapsulated dry weight [$= N(q + f)$]

α = fraction of film that is pore-former

β = (a) proportionality constant (granulation film thickness); (b) factor in non-sink condition

δ = diameter of holes

η = viscosity of saturated solution within the coated bead

ρ = (a) weighted density average of the dry solids in the coated beads; (b) general density term

ρ' = density of pore former

ϕ = a constant in nonsink condition $= [DA/(V\beta^*)]$

REFERENCES

- Acikgoz M, Kas HS, Orman M, Hincal AA (1996). *J Microencapsul* 13:141.
- Bavin PMG, Post A, Zarembko JE (1984). In: Florey KI, ed. *Analytical Profiles of Drug Substances*, vol 13. Academic Press, Orlando, FL, pp 128–180.
- Bennett CA, Franklin NJ (1961). In: *Statistical Analysis in Chemistry and the Chemical Industry*. p 71. John Wiley, New York, NY.
- Belleville M, Merie F, Lechevin JC (1979). U. S. patent 4,155,993.
- Biancini R, Vecchio C (1989). *Il Farm* 44:645.
- Biancini R, Bruni G, Gazzamoga A, Vecchio C (1993). *Drug Dev Ind Pharm* 19:2021.
- Carstensen JT (1996). *Modeling and Data Treatment in the Pharmaceutical Sciences*. Technomic Publishing, Lancaster, PA, p 32.
- Chwala A, Taylor KMG, Newton JM, Johnson MCR (1994). *Int J Pharm* 108:233f.
- Conte U, Giunchedi P, Maggi L, Torre ML (1994). *J Pharm Biopharm* 40:203.
- Guyot M, Fawaz F (1998). *Int J Pharm* 175:61.
- Hassan EE, Parish RC, Gallo JM (1992). *Pharm Res* 9:190.
- He P, Davis SS, Illum L (1998). *Int J Pharm* 166:75.
- He P, Davis SS, Illum L (1999). *Int J Pharm* 187:53.
- Hermelin V (1963). U. S. patent 3,115,441.
- Hsiao (1985). U. S. patent 4,555,399.
- Hsiao (1987). U. S. patent 4,634,587.

- Lippold H, Sutter K, Lippold BC (1989). *Int J Pharm* 54:15.
- Palmeri BF, Wehrle P (1997). *Drug Dev Ind Pharm* 20:2859.
- Palmeri BF, Wehrle P, Stamm A (1994). *Drug Dev Ind Pharm* 20:2859.
- Porter C (1990). *Drug Dev Ind Pharm* 15:1495.
- Powel TC (1971). U. S. patent 3,623,997.
- Rork GS, Haslam JL (1994). International Patent Application WO 94/01093.
- Rowe RC (1986). *Int J Pharm* 29:37.
- Santinho AJP, Pereira NL, de Freitas O, Collett JH (1999). *Int J Pharm* 186:191.
- Yang T, Van Savage G, Weiss J, Ghebre-Selassie J (1992). *Int J Pharm* 86:247.
- Yuen KH, Desmukh AA, Newton JM (1997). *Drug Dev Ind Pharm* 19:855.

RECOMMENDED READING

- Bakan JA (1986). In: Lachman L, Lieberman HA, Kanig JL, eds. *The Theory and Practice of Industrial Pharmacy*, 3rd ed. Lea & Febiger, Philadelphia, pp 412–429.

Index

- Adsorption, isosteric heat of, 74
- Adsorption isotherms, 66–74
 - BET, 69–74
 - Freundlich, 67
 - hysteresis, 75
 - Langmuir, 67–69
 - types I-IV, 66
- Adsorption models, assumptions for, 75
- Alginic acid, 449
- Amorphates, 107–116
 - crystallization rates of, 112–118
 - determination of amorphate content, 112
 - hydrous, 176
 - hydrous, as solution systems, 110
 - kinetics of decomposition of, 224–228, 268
 - methods of preparation, 108, 109
- Amorphous cakes, 176
- Amorphous indomethacin, 225
 - decomposition of, 225–227
- Amorphous solid, 2
- Amoxicillin
 - amorphous anhydrate, 108
 - trihydrate, 108
- Andreasen apparatus, 58
- Angle of repose, 302–303
 - flow rates correlated to, 315
- Apparent density
 - of binary mixtures, 283–285
 - definitions, 282
 - of powder beds, 281–296
- Apparent volumes of powders, 281–296
- Asperite melting, 411–413
- Athy–Heckel equation, 393–394, 421
- Average particle size from dissolution
 - profiles, 210–217
- Avrami–Erofeyev Equations, 122–123, 230–234, 247
- Ball mills, 324–327
- Bawn model, 240–245
- BET isotherm, 69–74
- Binder, 354–355
- Binomial distributions, applied to
 - mixtures, 336–338
- Blending, 335–352
- Brittle fracture
 - in milling, 324
 - in tableting, 383
- Buffers, effect on solid state stability, 277–278
- Buoyancy tablets, 486
- CAP (cellulose acetate phthalate), 449
- Capping, 419–420
- Carman–Kozeny equation, 78–79
- Cellulose, 441–442
- Cellulose acetate derivatives, 449
- Cellulose derivatives, 441–442
- Chitosan, 414
- CMC (carboxymethylcellulose), 449
- Coated non-pareils, 498–499
- Coating for sustained release, 496–498
- Coating of tablets, 455–467
 - enteric coating, 457
 - film coating, 456–459
- Cogrinds, 186
- Cohesion, 299–307
 - measurement of, 303–306
 - in powder beds, 301–303
 - and repose angles, 302–303
 - role in mixing, 343
 - for two particles, 300

- Comminution, 323–334 (*see also* Milling)
- Compaction of powder beds, 295–296
- Complexation, 41, 42
- Complex formation
 - between drug and polymer, 477
 - effect on dissolution, 219–220
- Compression-coated tablets, 435
- Compression cycles, 396–398
- Condensation kinetics, 140–142
- Contact angle, importance in granulation, 357
- Contact points in solid state kinetics, 257–261
- Cooper–Eaton equation, 394–396
- Coprecipitates, 185
- Coprecipitation, for producing continuous films, 503
- Coulter counter, 56
- Critical compression force, 420
- Critical dissolution time from dissolution data, 217–219
- Critical moisture content, 142–144
- Critical nucleus size, 91
- Critical temperature for hydrates, 148–150
- Critical time in Bawn model, determination of, 242
- Crushing strength of tablets, 418–419
- Crystal growth, 95
- Crystal growth rate, 95
- Crystal habit, 104–105
 - of polymorphs, 126
- Crystallization rates of amorphates, 112–114
- Crystalline solid, 2
 - determination of percent amorphate in, 112
- Crystallization, 89–108
 - cooling curves in, 101
 - effect of impurities, 94
 - and equilibrium crystal size, 92
 - product yield, 94
 - reaction rate, 96
 - resulting particle size distributions from, 96–100
 - and supersaturation, 90
 - thermal, particle size distributions from, 102–104
- Crystal Systems, 4,5
- Cyclodextrins, 42
- Defects in direct compression tablets, 416
- Dehydration of amoxicillin trihydrate, 108
- Dehydration kinetics, 167
 - as a function of water vapor pressure, 167
- Dehydration of theophylline, 234
- Density, 16
 - definitions, 282
 - determination of, 17
 - of powder beds, 281–296
 - substituent effect, 18
 - use in defect determination, 16
- Diameter definitions, 62, 63
- Dielectric constant, effect on solubility, 38
- Diffuse reflectance IR, 58
- Diffusion controlled solid reactions, 245–249
- Diffusion through films, 446–448
- Direct compression tablets, 408
 - defects in, 416
 - dry binders, 414
 - effect of moisture on, 415–416
 - excipients for, 413
 - loading capacity, 409
 - mechanisms, 411
 - mixed excipients for, 415
 - particle size considerations, 409–410
- Disintegrants, 427–429
 - rate of water uptake of, 428
- Disintegration, 427–437
 - effect of tableting pressure on, 430
 - models for, 429–431
- Dissolution, 427–437
 - by calorimetry, 194
 - effect of temperature, 196
 - effect of viscosity, 196
 - Fick's law in, 196
 - film theory of, 195
 - from hard-shell capsules, 382
 - Hixson–Crowell equation, 198
 - Nelson–Shah equation, 197
 - non-sink, 194
 - from particles and surfaces, 191–206
 - of polydisperse powders, 200–202
 - shape factors and, 203–206
 - from tablets, 432–435
 - from wet-processed granules, 368–370
- Dissolution medium, effect on dissolution rate, 219
- Dissolution rates of polymorphs, 128
- Dissolution of solid dispersions, 186
- Distributions, 62
 - lognormal, 63–65

- Dosage form, 2
- Dosators, 379
- Drug, 2
- Drug substance, 2, 156–166
- Drug product, 2
- Dry binders, 414
- Drying, 164
 - of salt hydrates, 165–166
- DSC, 1
 - modulated, 110
- EC (Ethyl cellulose), 445
- Effervescent systems, stability of, 249–254
- Einstein equation, 19–21
- Elastic limit, during hard-shell filling, 381
- Electrolytes
 - effect on solubility, 37–38
- Enantiotropes, 119
 - melting points and vapor pressure curves of, 119–120
- Energy
 - considerations in tableting, 401–404
- Enteric coating, 457
- Enteric coating sustained release, 471
- Enthalpy, 2
- Equilibrium, effect in solid state reactions, 256
- Erosion tablets, 471–473
- Eutectic diagrams, 172–174
 - use of DSC in, 181
- Eutectic mixture, 180
- Eutectics, 169–189
- EVOP-method of optimization, 422–423
- Excipients for direct compression, 413–414
- Extragranular porosity, 362–363
 - effect of moisture content, 364
 - effect of temperature on, 363
 - fluid bed granulation, 364–366
- Ferret's diameter, 62
- Film coating, 456–459
 - defects, 457
 - of particulates for sustained release, 495–496
 - plasticizers for, 459
- Film coats
 - aqueous, 463–465
 - effect of storage on, 460
 - solvent systems for, 462–463
 - strength of, 460–462
 - sustained release, 465–467
- Film theory of dissolution, 195
- Floatable tablets, 486
- Flory-Higgins model, 111
- Flow rates
 - correlation with repose angle, 315–316
 - dynamic flow rates, 320
 - effect efflux tube diameter on, 318
 - effect of moisture on, 319
 - measurement of 311
 - of powders, 309–321
 - regularity of, 311
 - wall effects on, 316–318
- Fluid energy mills, 330
- Fourier-transform diffuse reflectance IR, 58
- Fractal dimensions, 81–85
- Free energy, 2
- Freeze drying, 176–178
- Freezing curves of ideal solutions, 170
- Frenkel defect, 14
- Freundlich isotherm, 67
- Friction, 299
 - measurement of, 303–306
- Frictional coefficient,
 - definition and measurement, 299–300
 - in tableting, 400
- FTIR, use in polymorphic identification, 118
- Gas adsorption, 54
- Gas phase interactions in solid state
 - kinetics, 261
- Gelatin, 449
- Gibbs energy, 2
- Gibbs' phase rule, 3
- Glass transition
 - for plasticizers, 460
 - Gordon-Taylor equation, 109
- Gordon-Taylor equation, 109
- Granulation, wet, 353–370
 - effect of water addition rate, 362
 - endpoints, 358–359
 - fluid bed, 364
 - pelletizing, 366–367
 - physics of, 358
- Granule
 - density, 359–361
 - dissolution from, 370
 - formation, 354
 - measurements of, 356–357
 - porosity of, 359
 - properties of, 356–357
 - size determination, 367–368

- [Granule]
 tensile strength, 357
 types of, 356
Guar gum, 449
- Hammer mills, 327–330
Hardness of tablets, 418–419
Hard-shell capsules, 375–385
 arriving at fill weights for, 380–381
 compaction during, 381
 disintegration of, 382–383
 dissolution from, 382
 dosator principle, 379
 effect of speed on fill weight, 378–379
 pelliculation of, 383
 sizes, 376
 as sustained release dosage forms, 384
 two-ring machine for making, 376–379
Hatch–Choate relations, 63–65
Heat capacity, 18–21
 classical, 18, 19
 Einstein model, 19–21
Heat of solution, 28–32
Heckel equation, 393–394, 421
Helmholz energy, 2
Higuchi square root law, 472
Hildebrand–Scott equation, 462
Hixson–Crowell equation
 effect of particle shape, 200
 for monodisperse powder, 198–199
Homogeneous nucleation, 93
 lag times in, 94
Hooke's law, 323
 applied to milling, 323–324
 in tablet formation, 391–393
Horsfield packing, 294
HPC (hydroxypropyl cellulose, 445–446
HPMC (hydroxypropyl methylcellulose), 444–445
 modified, 483
Hydrates, stability profiles, 276–277
Hydrodynamic diameter, 57
Hydrogels, 478–482
 effect of amount of polymer, 482
 effect of diluents, 482
 effect of drug loading, 482
 effect of molecular weight of polymer, 482
 erosion of, 479–482
 release and equations for, 484–485
 use of mixtures of polymers, 484
- Hydrous amorphates, 176
 Flory–Higgins model, 111
 as solution systems, 110–112
 Vrentas model, 111
Hygroscopicity, 134
Hysteresis
 in adsorption isotherms, 75
 in moisture isotherms, 153–156
- Immiscible melts, 178–179
Ink bottle pores, 359
IR, 1
 use in polymorphic identification, 118
Isomers, optical, 163–164
Isometric particle shape, 52
Isosteric heat of adsorption, 74
Isoviscosity curves, 177
- Jander equation, 247
Jenike
 locus, 303
 shear cell, 303
Johnson–Mehl–Avrami equation, 228
 crystallization of amorphous lactose and, 228
- Kinetics of decomposition of solids
 of benzoic acids, 224
 nearest neighbor effect, 225
Kinetics of noncohesive mixing, 343–346
 effect of particle size, 347
- Langmuir isotherm, 67–69
Largest particle size
 from dissolution profiles, 209–219
Lattice defects, 13
 energy of, 15–16
Lattices, 6
Lattice energy, 8–10
Levich equation, 197
Liquid, 2
Liquid interaction phases in solid state
 kinetics, 257–261
Liquidus line, 175
 using DSC to establish, 181
Lognormal distribution, 63–65
Lognormal distributed powders, dissolution
 from, 209, 210
Lubrication, in tablets, 400–401
Lyophilization, 176–178
- Macropores, 359

- Maltodextrins, 414
- Martin's diameter, 62
- Matrix tablets, 473–475
 - percolation theory pertaining to, 475–477
- Mean particle size
 - from dissolution profiles, 210–217
 - as a function of screen aperture in milling, 328
- MC (methylcellulose), 414
- MCC (microcrystalline cellulose), 414,
- Melting points, 23–24
 - of polymorphs, 24, 25
- Melting point depressions, 171
- Melting point diagrams, 169–189
 - of ideal solutions, 170
- Melts
 - immiscible, 178–179
 - miscible, 179–183
 - partially miscible, 183
 - solid dispersions, 184
- Mercury intrusion porosimetry, 76–79
 - pore size distribution from, 360
 - surface area from, 79, 361
 - for wet granules, 359–361
- Mesopores, 356
- Metastable zone, 90
- Micellar systems
 - effect on solubility, 44–45
- Microcapsules, 493–500
 - tableted, 504
- Microenvironmental pH, effect on solid state stability 254–255, 275–276
- Micromeritics, 61–88
- Micronizers, 330
- Micropores, 359
- Microscopy, 1, 53, 65
- Milling, 323–334
 - effect on particle size distribution, 330–332
 - optimum feed rate, 328
- Minimum particle size from dissolution profiles, 209–219
- Mixed polymorphs, 125, 127
- Mixed solvents
 - in purification, 161
- Mixing, 335–352
 - effect of particle size, 347
 - efficiency, 347
 - modes of sampling in, 338–340
 - of noncohesive powders, 341
- Modified HPMC, 483
- Mohr bodies, 398–400
- Moisture
 - bound moisture, 273–274
 - effect on extragranular porosity, 364
 - effect on stability of metastable polymorphs, 123–124, 129
 - effect on solid-state stability of, 267–279
 - effect on tensile strength of granules, 357
 - stability at the critical moisture content, 271–273
 - stability effect of excess water, 274–275
 - stability effect of intermediate moisture levels, 269
 - stability effect of very low moisture levels, 268–271
- Moisture exchange between excipients, 153–156
- Moisture isotherms
 - as BET isotherms, 136–138
 - for crystalline solids, 133–158
 - for hydrates, 145–148,
 - for large crystalline molecules, 138
 - for multiple hydrates, 150–153
 - for non-hydrates, 138–140
 - smooth, 153–156
- Moisture uptake rate, 134
- Molecular compounds, 174
- Molecular weights
 - and intrinsic viscosity, 442–443
 - of polymers, 440–441
- Monodisperse powders, 52
- Monotropes, 119
 - melting points and vapor pressure curves of, 119–120
- Morphology
 - effect on dissolution, 89
- Mortar and pestle, 325
- Multilayer tablet machines, 390, 438
- Multiparticulates, 52
- Ng equation, 234, 239–240
- Noncohesive mixing, kinetics of, 343–346
- Non-segregating mixtures, 288–290
- Non-sink dissolution, 194
 - in microcapsules, 505–507
- Normal distribution, 65
 - Z-value, 65
- Noyes-Whitney equation, 191
- Nucleation, 91, 100
 - homogeneous, 93
- Nucleation rates in Amorphates 107–108

- One-component systems, 1
- Optical isomers, 163–164
- Ordered mixing, 348–350
- Osmotic pumps, 485–486
- Ostwald–Freundlich equation, 51, 92
- Packing
 - closest, 285–286
 - Horsfield, 294
- Particle diameters, 51–61
 - by Andreasen apparatus, 58
 - arithmetic mean, 56
 - electronic counters for, 56
 - hydrodynamic, 57
 - related to shapes, 58
 - surface mean, 57
 - surface volume mean, 55
 - volume mean, 57
- Particle dimensions, 52
- Particle shape, 58
 - effect on machinability, 89
- Particle size, 51–61
 - effect in direct compression tablets, 409–410
 - effect on flow rate, 314
 - effect on mixing, 347
 - measurement, 53
 - and solubility, 46
- Particle size distributions
 - from dissolution, 210–217
 - after homogeneous crystallization, 96–100
 - log normal after milling, 330–332
 - surface area determination from, 79
- Particle size enlargement, effect on flow rate, 319
- Partly miscible melts, 183
- PEGs (Polyethylene glycols), 441
- Pelletizing, 366–367
- Pellets, dissolution patterns from, 367
- Pelliculation, 383
- Percolation theory, 475–477
- Permeametry, 54, 79
- pH
 - effect in solid state kinetics, 254–255
 - effect on solubility, 42–44
- Plasticizers, 448–449
 - in film coating, 459–460
- Plastic deformation
 - in milling, 324
- Poisson ratio, in tablet formation, 393–394
- Polydisperse powders, 52
 - dissolution from, 209–219
 - flow rate of, 319
- Polymers, 114, 439–450
 - molecular weight determination, 440–441
 - pH and temperature sensitive, 450–451
- Polymethacrylates, 444
- Polymorphism, 7, 24–25, 117–130
 - methods of detection, 118
 - pharmaceutical significance, 117
- Polymorphs
 - dissolution rates of, 126–129
 - effect of moisture on transformation of, 123–125
 - methods of preparation, 118
 - mixed, 125, 127
 - moist storage, effect on, 129
 - solubility of, 35–37
 - solubility and thermodynamic functions, 126–127
 - stability of, 121–123
- Polysaccharides, 449
- Porosity
 - from adsorption isotherms, 75–76
 - extragranular, 362
 - measurement, 359–361
- Porosity of powder beds
 - correlation with bed density, 282
 - definition, 282
 - of multiparticulate, multidisperse mixtures 291–294
- Powder flow, 309–321
 - definitions, 310–311
 - of polydisperse powders, 319
 - regularity of, 311
 - static, 310
 - in tableting, 312–313
 - types of, 313–314
- Precipitation
 - by pH-Change, 160
- Premixing, 346
- Pressure effect in solid state reactions, 256
- Prout–Tompkins equation, 234–238, 247, 269
- Pseudopolymorphic transformations, 255
- Pseudopolymorphism, 125
- Purification, 89
 - by mixed solvent technique, 161
 - by pH-change, 160
 - by thermal recrystallization, 162
- Purity assessment from melting point depression, 171

- PVP (polyvinyl pyrrolidone), 444
- P-X diagrams
for compounds forming more than one hydrate, 150–153
for hydrates, 145–148
- Radius ratio rule, 6
- Random decomposition in solids, 224–228
- Recrystallization, thermal, 102–104, 162
- Repose angle, 302–303, 311
flow rates as a function of, 315
- Reprecipitation, 90
- Residual standard deviation of powder mixes, 337
- Roller compaction, 417
- Rotary tablet machines, 389–390
- Salt hydrates
drying of, 165–166
equilibrium moisture content, 144–145
- Salt selection, 160
- Sampling thief, 339
validation of, 350
- Schottky defect, 14
- Screw defect, 14
- Segregation of noncohesive powders, 340
- SEM, 54
- Shape factors, 79–81
during dissolution, 202–206
from dissolution profiles, 210–217
from fractal dimensions, 81–85
surface mean shape factor, 79
volumetric mean shape factor, 79
- Sieve analysis, 55
- Sieve test, 367–368
- Silica gel, 134
- Single punch tablet machines, 388–380
- Sink conditions, 193
- Slugging, 417
- Smallest particle size from dissolution profiles, 209–219
- Sodium starch glycolate, 449
- Solid, 2
properties of, 13
- Solid dispersions, 184
dissolution of, 186
- Solid solutions, 175–176, 183
of the first kind, 182
of the second kind, 184
- Solid state stability, 213–265
diffusion controlled, 245–249
[Solid state stability]
by nucleation followed by fast reaction, 234
by surface nucleation, 234–238
- Solid to liquid-plus gas reaction, 240–245
temperature dependence of, 238–239
- Solid to solid-plus-gas reaction, 235–238
- Solidus line, 175
- Solubility, 27–49
determination of, 32
effect of complexation, 41, 42
effect of dielectric constant, 38
effect of electrolytes, 37–38
effect of particle size, 46
effect of pH, 42–44
effect of solvents, 37
multiple peaks, 39–41
of optical isomers, 163–164
of polymorphs, 35–37, 124, 126–127
of poorly stable substances, 45–46
prediction of, 44
temperature, effect on, 32–37
- Solubility parameters, 38
- Solvates, drying of, 167–168
- Solvents, effect on solubility, 37
- Spheronization, 370
- Spreading coefficient, 357
- States of matter, 2
- Statistics of ideal mixtures, 336–338
- Stokes–Einstein equation, 196
- Stokes law, 57
- Stress and strain in tablet formation, 391
- Subsieve sizer, 54
- Sugar coating, 456
- Surface areas
from mercury porosimetry, 78
from particle size distributions, 79
- Surface mean diameter, 57
- Surface volume mean diameter, 54, 55
- Surfactants, effect on solubility, 46
- Sustained release
by chemical modification, 470
by coated particles, 496–498
EC films in, 504–505
effect of film-thickness on, 501–502
by enteric coating, 471
equations for, 486–487
by erosion, 471
film coats, 465–467
films used for, 507–508
hard-shell capsules, 384
by hydrogels, 476–477

[Sustained release]

- by microencapsulatin, 493–508
- by multiple film-thickness, 501–502
- by multiple osmotic pumps, 499–501
- by non-pareils, 498–499
- percolation theory pertaining to, 475–477
- single unit dosage forms, 469–483
- by sized particles, 494
- use of mixed and multiple films in, 503

Tablet coating, 455–467**Tablets**

- asprite melting as bonding in, 411–413
- bonding types in, 421–422
- brittle fracture mechanism, 383
- capping of 418–419
- capping pressure, 420
- coating of, 455–467
- compression coated, 435
- compression cycles, 396–398
- critical compression force, 420
- direct compression, 408–411
- energy consumption for, 401–404
- hardness test for, 418
- lubrication, 400–401
- multilayer, 390, 438
- optimization of, 422–423
- physical principles of, 407–420
- roller compaction for, 417
- rotary machines, 389–390
- single punch machines, 388–380
- slugging for, 417
- stress and strain in, 391
- tensile strength of, 418–419
- uniaxial expansion of, 420–421
- wet granulated, 416
- yield value, 381–383

Tablet physics, 387–404**Tapped density, 295****Tartaric acid-sodium bicarbonate system, 249–254****Temperature of granulation, effect on granule porosity, 363****Tensile Strength of Tablets, 418–419****TGA, 1****Thermal recrystallization, 162**

- particle size distribution from, 102

Thermodynamic functions, 2**Topochemical reactions, 228–230****Transformation of polymorphs**

- rates and models of, 121–123

Unstable compounds, determination of stability of, 46**Validation of sampling thief, 350****Van Laar equation, 171–172****Vapor pressure**

- of hydrates, 145–148
- of solids, 22,23

Vrentas model, 111**Wall effects**

- effects on flow rates, 316–318
- in powder beds, 286–288
- for spheres, 290

Water adsorption

- into amorphates, 110–112

Wet granulation, 353–370, 416

- equipment, 354
- flow sheet, 354
- particle enlargement, 354

Wood's Apparatus, 192

- effect of variables, 194–195

Yield value

- in milling, 324
- in tablets, 383

Young's modulus, of capsule fills, 381**X-ray****X-ray crystallography, 4****X-ray diffraction, 1, 5****Xylitol, 414**